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L2 29 PERMEABILITY AND BRAIN AND DELIVER

=> s l1 and l2
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L4 0 L1 AND PERMEABLILITY

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L5 6 L1 AND PERMEABILITY

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L6 6 DUP REM L5 (0 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 2001:564822 CAPLUS
DN 135:132469
TI Method for using potassium channel activation for delivering a medicant to an abnormal brain region and/or a malignant tumor
IN Black, Keith L.; Ningaraj, Nagendra S.
PA Cedars-Sinai Medical Center, USA
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001054680	A2	20010802	WO 2001-US2742	20010126

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-491500 A 20000126
US 2000-615854 A 20000714

AB Disclosed are methods of selectively delivering a medicant to an abnormal brain region and/or to a malignant tumor in a mammalian subject, including a human. A medicant is administered simultaneously or substantially simultaneously with a calcium- or ATP-dependent potassium channel [KCa or KATP] activator (other than bradykinin or a bradykinin analog), such as a direct potassium channel agonist or an indirect ***potassium*** ***channel*** ***activator*** , such as an activator of sol. guanylyl cyclase (e.g., nitric oxide or a nitric oxide donor) or an activator of cGMP-dependent protein kinase, whereby the medicant is delivered selectively to the cells of the abnormal brain region and/or to the tumor, compared to normal tissues. Thus, among the disclosures is a method of treating a malignant tumor in a human subject. Also disclosed are pharmaceutical comps. that combine a ***potassium*** ***channel*** ***activator*** together with a medicant and a kit for enhancing the delivery of a medicant to an abnormal brain region and/or to a malignant tumor.

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L6 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:185630 BIOSIS
DN PREV199800185630
TI Effect of K+ channel openers on K+ channel in cultured human dermal papilla cells.
AU Hamaoka, Hiroyasu; Minakuchi, Kazuo; Miyoshi, Hirokazu; Arase, Seiji; Chen, Chun-He; Nakaya, Yutaka (1)
CS (1) Dep. Nutr., Univ. Tokushima Sch. Med., 3-18-15 Kuramoto-cho, Tokushima 770 Japan
SO Journal of Medical Investigation, (Aug., 1997) Vol. 44, No. 1-2, pp. 73-77.
ISSN: 1343-1420.
DT Article
LA English
AB Minoxidil sulfate and pinacidil, well-known activators of the ATP-sensitive K+ (KATP) channel, induce hair growth in clinical studies. The opening of K+ channels is thought to be an important mechanism in the regulation of hair follicles. In the present study, we used the patch clamp technique to characterize the K+ channels and tested the effect of K+ channel openers on K+ channels in cultured human dermal papilla cells. In dermal papilla cells, the Ca2+-activated K+ (KCa) channel with large conductance (179.3 +- 13.1 pS in symmetrical 150 mM K+ solutions, n=9) was dominant and we could not observe KATP channels in cell-attached and inside-out patches. In addition, minoxidil and pinacidil failed to activate KATP or KCa channels. In inside-out membrane patches, the channel was blocked by 10 mM tetraethylammonium ion, 2 mM 4-aminopyridine to the cytosolic face of the membrane or by lowering Ca2+ using 10 mM EGTA, but not by glibenclamide. In the cell-attached patch configurations, extracellular application of 1 MM sodium nitroprusside, a nitrovasodilator, activated the KCa channel. Methylene blue (2 mM inhibited channel activation by sodium nitroprusside. Extracellular application of 20 mM dibutyryl cGMP activated the KCa channel, suggesting that channel activation is mediated by cGMP. Nitrovasodilators, which have no effect on hair growth, now appear to activate KCa channels in dermal papilla cells. These results suggest that increased K+ ***permeability*** itself in dermal papilla cells may not be sufficient for promotion of hair growth.

L6 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1990:265684 BIOSIS
DN BA90:7770
TI EFFECTS OF PINACIDIL ON ISOLATED HUMAN CORPUS CAVERNOSUM PENIS.
AU HOLMQUIST F; ANDERSSON K-E; HEDLUND H
CS DEP. CLINICAL PHARMACOL., UNIV. HOSP., S-221 85 LUND, SWEDEN.
SO ACTA PHYSIOL SCAND, (1990) 138 (4), 463-470.
CODEN: APSCAX. ISSN: 0001-6772.
FS BA; OLD
LA English
AB Intracavernous injection of vasoactive agents causing vasodilatation is widely recognized in the diagnosis and treatment of erectile dysfunction. However, papaverine, the drug most commonly used for this purpose, may produce priapism and fibrotic lesions, and alternatives without these disadvantages are desirable. In this study we investigated the effects of pinacidil, a vasodilator drug supposed to act through the opening of K-channels, on isolated human corpus cavernosum penis. Besides abolishing spontaneous contractile activity, pinacidil effectively relaxed preparations precontracted by noradrenaline 10-6 M and inhibited contractions induced by electrical field stimulation of nerves. Furthermore, pinacidil depressed contractions induced by low-K+solutions (.Itoreq. 20 mM) and concentration-dependently increased the efflux of 86Rb from preloaded tissue. The results suggest that pinacidil is effective in relaxing isolated human erectile tissue, probably by way of increased K+ ***permeability*** and subsequent hyperpolarization. Clinical testing seems justified in order to find out if K+-channel openers can be used in the pharmacological treatment of impotence.

L6 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1991:469220 CAPLUS
DN 115:69220
TI Endothelium-derived hyperpolarizing factor (EDHF): an endogenous ***potassium*** - ***channel*** ***activator***
AU Suzuki, Hikaru; Chen, Guifa
CS Med. Sch., Nagoya City Univ., Nagoya, 467, Japan
SO News Physiol. Sci. (1990), 5(Oct.), 212-15
CODEN: NEPSEY; ISSN: 0886-1714
DT Journal
LA English
AB In studies on rat aorta, acetylcholine hyperpolarizes the membrane of vascular smooth muscles by increasing K+ ***permeability*** , the response being mediated by an endothelium-derived hyperpolarizing factor (EDHF). The membrane hyperpolarization produced by EDHF is therefore one of the components contributing to endothelium-dependent relaxation of vascular smooth muscles.

L6 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1989:319470 BIOSIS
DN BA88:33200
TI THE EFFECTS OF CROMAKALIM ON THE DETRUSOR MUSCLE OF HUMAN AND PIG URINARY
BLADDER.
AU FOSTER C D; SPEAKMAN M J; FUJII F; BRADING A F
CS UNIV. DEP. PHARMACOLOGY, SOUTH PARKS ROAD, OXFORD OX1 3QT.
SO BR J UROL, (1989) 63 (3), 284-294.
CODEN: BJURAN. ISSN: 0007-1331.
FS BA; OLD
LA English
AB The effects of cromakalim, a potassium channel activating drug, have been studied on isolated detrusor muscle strips from normal Landrace boar, normal and unstable mini-pig and unstable human bladder. Cromakalim abolished spontaneous activity in all strips but did not abolish the ability of the detrusor muscle from any of the specimens studied to respond to carbachol, increased extracellular K+ or transmural nerve stimulation. Intravenous infusion of cromakalim in the urethral obstructed mini-pig caused the characteristic unstable contractions associated with bladder outflow obstruction to be abolished, leaving the animal able to void. Experiments with potassium isotopes and the sucrose gap technique demonstrated that cromakalim increased the potassium ***permeability*** and hyperpolarised the cell membrane, consistent with its reported actions on other smooth muscles. These results suggest that drugs such as cromakalim, which act by reducing membrane excitability without inhibiting responses to existing innervation, may have a clinical application in the treatment of instability which is secondary to bladder outflow obstruction.

L6 ANSWER 6 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 89119279 EMBASE
DN 1989119279
TI Endothelin-1-induced contractions of vascular and tracheal smooth muscle: Effects of nicardipine and BRL 34915.
AU Turner N.C.; Dollery C.T.; Williams A.J.
CS Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, United Kingdom
SO Journal of Cardiovascular Pharmacology, (1989) 13/SUPPL. 5 (S180-S182). ISSN: 0160-2446 CODEN: JCPCDT
CY United States
DT Journal
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Endothelin-1 (ET-1) produced concentration-dependent contractions of rat aorta and rat trachea. These contractions were dependent on the presence of extracellular calcium but unaffected by nicardipine. Contractions of aorta could be attenuated with the ***potassium*** ***channel*** ***activator*** BRL 34915. BRL 34915 also elicited dose-related relaxations of rat aorta and trachea precontracted with ET-1. We conclude that although the increase in calcium ***permeability*** elicited by ET-1 may not involve dihydropyridine-sensitive calcium channels, its reversal by BRL 34915 suggests that smooth muscle contraction by ET-1 may involve a voltage-linked mechanism.

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L1 ANSWER 1 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:509497 BIOSIS
DN PREV200100509497
TI Diazoxide, but not cyclosporin A or hypothermia, preserves N-methyl-D-aspartate (NMDA)-induced cerebral dilation after ischemia in piglets.
AU Busija, D. W. (1); Perciaccante, J. (1); Domoki, F. (1)
CS (1) Physiology/Pharmacology, Wake Forest Univ. School of Medicine, Winston-Salem, NC USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 887. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DT Conference
LA English
SL English
AB We have previously shown that diazoxide, a specific activator of mitochondrial ATP-sensitive potassium channels (mKATP), preserves vascular dilator responses to application of NMDA after ischemia (Stroke 30:2713-2718, 1999). We also have shown that diazoxide administration limits infarct volume in neonatal and adult rats following cerebral ischemia. In addition, other interventions that affect mitochrondial function, such as cyclosporin A (CsA) administration and brain cooling, also reduce infarct size after ischemia. Thus, we assessed whether CsA and hypothermia were as effective as diazoxide in protecting neuronal function against ischemia. We examined effects of NMDA in anesthetized piglets on pial arteriolar diameter before ischemia and 1 hour after 10 min of global ischemia in three groups: diazoxide pretreated (10-5M; n=5), CsA pretreated (10-4M; n=6), and local brain cooling (34degreeC; n=11). Total brain ischemia was induced by increasing intracranial pressure. In the diazoxide group, arterioles (baseline diameterapprx100 microns) dilated by 15+-9% versus 14+-5% at 5X10-5M NMDA (ns) and by 41+-13% versus 39+-8% at
10-4M NMDA (ns), before and after ischemia, respectively. In the CsA group, arteriolar dilation was reduced (p<.05) by ischemia to 6+-4% at 5X10-5M NMDA and 13+-8% at 10-4M NMDA. In the hypothermia group, dilation
was reduced to 8+-5% at 5X10-5M NMDA and 20+-5% at 10-4M NMDA after ischemia (p<.05). We conclude that diazoxide has specific neuroprotective effects via KATP on neuronal function in the early post-ischemic period.

L1 ANSWER 2 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:500005 BIOSIS
DN PREV200100500005
TI Hologram QSAR analysis of benzopyrane type modulators of multidrug resistance.
AU Ecker, Gerhard F. (1); Wetwitayaklung, Penpun (1); Chiba, Peter
CS (1) Institute of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, Vienna, A-1090: gerhard.f.ecker@univie.ac.at, penpun@speedy.pch.univie.ac.at Austria
SO Abstracts of Papers American Chemical Society, (2001) Vol. 222, No. 1-2, pp. COMP140. print.
Meeting Info.: 222nd National Meeting of the American Chemical Society Chicago, Illinois, USA August 26-30, 2001 American Chemical Society
. ISSN: 0065-7727.
DT Conference

LA English
SL English

L1 ANSWER 3 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:497824 BIOSIS
DN PREV200100497824
TI Characterization of a large-conductance calcium-activated potassium channel in Aplysia bag cell neurons.
AU Zhang, Y. (1); Magoski, N. S. (1); Kaczmarek, L. K. (1)
CS (1) Dept Pharmacol, Yale Univ Sch Med, New Haven, CT USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 709. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DT Conference
LA English
SL English
AB Large-conductance, Ca2+-activated potassium channels (maxi-K) are found in many neurons and shape a variety of electrical properties. Maxi-K current is gated by both intracellular Ca2+ as well as membrane depolarization, and is a significant component of the outward current both in somata and at axonal endings - the site of transmitter release. We have begun a characterization of maxi-K in the bag cell neurons of Aplysia, a group of identified neurons that controls egg-laying behavior and serves as a model for the study of excitability and neuropeptide secretion. We recorded maxi-K in cultured bag cell neurons under whole-cell voltage-clamp, in Ca2+-and Na+-free extracellular solution. When intracellular Ca2+ was set at 1 muM, large, outwardly rectifying currents were observed from a holding potential of -60 mV. Omission of Ca2+ from the internal solution reduced the outward current, particularly at more positive voltages. The maxi-K activator, phloretin, produced a reversible, apprx33% enhancement of outward current, while paxilline, a specific maxi-K blocker, caused a reversible, apprx30% inhibition. The effects of both phloretin and paxilline were only observed when Ca2+ was present in the internal solution. We also examined the contribution of maxi-K to excitability by monitoring the effect of paxilline on action potentials recorded under sharp-electrode current-clamp. Paxilline increased both the height and width of the spike, suggesting that maxi-K plays a role in bag cell neuron excitability. Maxi-K may also serve to regulate peptidergic secretion from the bag cell neurons.

L1 ANSWER 4 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:468532 BIOSIS
DN PREV200100468532
TI Therapeutics for diabetic complications.
AU Koga, Hiroshi (1)
CS (1) Tokyo Japan
ASSIGNEE: Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan
PI US 6218411 April 17, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (Apr. 17, 2001) Vol. 1245, No. 3, pp. No Pagination. e-file.
ISSN: 0098-1133.
DT Patent
LA English
AB An agent for treating or ameliorating diabetic complications which contains at least one ***potassium*** ***channel*** ***activator*** as an active ingredient. The drug is expected to show a therapeutic or ameliorating action on diabetic complications such as retinopathy, neuropathy, nephropathy, peripheral circulation disorders, and skin ulcerations; it also proves effective in preventing, ameliorating, alleviating and gaining recovery from various symptoms and abnormalities caused by those diseases, as exemplified by blindness, proteinurea, pain, numbness, psychroesthesia, intermittent claudication and gangrene.

L1 ANSWER 5 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:367196 BIOSIS
DN PREV200100367196
TI KATP channels predominantly regulate conduit vessel tone in normoxic cat pulmonary arteries in vivo.
AU Shirai, Mikiyasu (1); Shimouchi, Akito; Mori, Hidezo; Nagaya, Noritoshi; Nakanishi, Norifumi; Kyotani, Shingo; Oya, Hideo; Ikeda, Soichiro; Min, Kyong-Yob; Ninomiya, Ishio
CS (1) Department of Cardiac Physiology, National Cardiovascular Center Research Institute, 5-7-1 Fujishiro-dai, Suita, Osaka, 565-8565: mshirai@ri.ncvc.go.jp Japan
SO European Journal of Pharmacology, (22 June, 2001) Vol. 422, No. 1-3, pp. 181-184. print.
ISSN: 0014-2999.
DT Article
LA English
SL English
AB Through our investigations of the intact pulmonary circulation, we aimed to find out whether KATP channels contribute to regulating basal vascular tone and to clarify which vascular segments dilate during KATP channel activation under basal tone conditions. Using an X-ray television system on anesthetized cat lungs, we measured internal diameter (ID) responses to two KATP channel inhibitors (glibenclamide and 4-morpholinecarboximidine-N-1-adamantyl-N'-cyclohexyl-hydrochloride (U-37883A)) and to an activator (levcromakalim) in normoxic pulmonary arteries. In conduit arteries (800-3000 mum ID), the inhibitors and activator induced larger ID constrictions (14-17%) and dilatations (29-32%), respectively. However, in resistance arteries (<500 mum), the constriction response was negligible and the dilatation response relatively small (5-10%). The data suggest that KATP channels are active and capable of regulating basal vascular tone primarily within conduit pulmonary arteries even though these channels are present in all pulmonary arteries.

L1 ANSWER 6 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:308730 BIOSIS
DN PREV200100308730
TI Cardioprotective effects of KR-31378, a cardioselective ATP-sensitive ***potassium*** ***channel*** ***activator*** , in rats and dogs.
AU Lee, Byung Ho (1); Seo, Ho Won (1); Yoo, Sung-Eun (1); Shin, Hwa Sup (1)
CS (1) Screening and Toxicology Research Center, Korea Research Institute of Chemical Technology, No. 100 Jangdong, Yusong, Taejon, 305-606 South Korea
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A568. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB The cardioprotective effects of KR-31378, a cardioselective ATP-sensitive ***potassium*** ***channel*** ***activator*** , were evaluated in rat and dog models of coronary artery occlusion and reperfusion. In addition, hemodynamic profiles of KR-31378 were compared with those of BMS-191095. In rats subjected to 45-min coronary occlusion and 90-min reperfusion, KR-31378 (bolus i.v., 30 min before ischemia) reduced infarct size from 60.8 +- 2.7% of the area at risk in controls to 36.6 +- 4.1 and 34.3 +- 1.2% for 0.3 and 1.0 mg/kg, respectively ($p<0.05$). The reduction in infarct size afforded by KR-31378 was inhibited by pretreatment with glibenclamide and sodium 5-hydroxydecanoate, selective ATP-sensitive potassium channel antagonists. In dogs that underwent 2-h occlusion followed by 4.5-h reperfusion, KR-31378 (i.v. infusion of 2 mg/kg over 40 min, starting 10 min before ischemia) markedly reduced infarct size from 48.7 +- 1.4% in controls to 19.1 +- 6.5 ($p<0.05$). In conscious rats, KR-31378 increased blood pressure only at high dose (20% at 100 mg/kg), unlike BMS-191095 that dose-dependently decreased blood pressure (33% at 3 mg/kg). In anesthetized dogs, KR-31378 was about 100-fold less potent than BMS-191095 for most hemodynamic parameters including blood pressure (i.v. ED20 values in decreasing blood pressure: 49.7 and 0.36 mg/kg, respectively), left ventricular pressure, +dP/dtmax and coronary flow, despite similar hemodynamic profiles to BMS-191095. These results indicate that KR-31378 is a potent cardioprotective agent with potentially minimal hypotensive effects. Thus, it could be useful in the prevention and treatment of acute myocardial infarction.

L1 ANSWER 7 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:307857 BIOSIS
DN PREV200100307857
TI BK channels in human glioma cells.
AU Ransom, Christopher B.; Sontheimer, Harald (1)
CS (1) Dept. of Neurobiology, University of Alabama, 1719 6th Ave. S., CIRC 545, Birmingham, AL, 35294: hws@nrc.uab.edu USA
SO Journal of Neurophysiology (Bethesda), (February, 2001) Vol. 85, No. 2, pp. 790-803. print.
ISSN: 0022-3077.
DT Article
LA English
SL English
AB Ion channels in inexcitable cells are involved in proliferation and volume regulation. Glioma cells robustly proliferate and undergo shape and volume changes during invasive migration. We investigated ion channel expression in two human glioma cell lines (D54MG and STTG-1). With low (Ca2+)i, both cell types displayed voltage-dependent currents that activated at positive voltages (more than +50 mV). Current density was sensitive to intracellular cation replacement with the following rank order; K+ > Cs+ apprxeq Li+ > Na+. Currents were >80% inhibited by iberiotoxin (33 nM), charybdotoxin (50 nM), quinine (1 mM), tetrandrine (30 muM), and tetraethylammonium ion (TEA; 1 mM). Extracellular phloretin (100 muM), an activator of BK(Ca2+) channels, and elevated intracellular Ca2+ negatively shifted the I-V curve of whole cell currents. With 0, 0.1, and 1 muM (Ca2+)i, the half-maximal voltages, V0.5, for whole cell current activation were +150, +65, and +12 mV, respectively. Elevating (K+)o potentiated whole cell currents in a fashion proportional to the square-root of (K+)o. Recording from cell-attached patches revealed large conductance channels (150-200 pS) with similar voltage dependence and activation kinetics as whole cell currents. These data indicate that human glioma cells express large-conductance, Ca2+-activated K+ (BK) channels. In amphotericin-perforated patches bradykinin (1 muM) activated TEA-sensitive currents that were abolished by preincubation with bis-(o-aminophenoxy)-N,N,N',N'-tetraacetic acid-AM (BAPTA-AM). The BK channels described here may influence the responses of glioma cells to stimuli that increase (Ca2+)i.

L1 ANSWER 8 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:284554 BIOSIS
DN PREV200100284554
TI Deterioration of the protein kinase C-KATP channel pathway in regulation of coronary flow in hypercholesterolaemic rabbits.
AU Pongo, Eva; Balla, Zsolt; Mubagwa, Kanigula; Flameng, Willem; Edes, Istvan; Szilvassy, Zoltan (1); Ferdinandy, Peter
CS (1) Department of Pharmacology, Medical University of Debrecen, Nagyerdei

krt. 98, H-4032, Debrecen: szilva@king.pharmacol.dote.hu Hungary
SO European Journal of Pharmacology, (27 April, 2001) Vol. 418, No. 3, pp. 217-223. print.
ISSN: 0014-2999.
DT Article
LA English
SL English
AB We studied the effect of experimental hypercholesterolaemia/atherosclerosis on changes in coronary flow and cardiac function, induced by protein kinase C and ATP-sensitive K+ (KATP) channel modulators in isolated Langendorff-perfused rabbit hearts. Both phorbol 12-myristate-13-acetate (PMA) and phorbol 12,13-dibutyrate (PDB, 0.1 muM each), activators of protein kinase C, decreased, whereas staurosporine, (0.1 muM), a protein kinase C inhibitor, increased coronary flow and left ventricular dP/dt, an index of ventricular contractility. Glyburide (5-50 muM), a KATP channel inhibitor, blocked the effect of staurosporine. The phorbol esters were without effect in the presence of pinacidil (5 muM), a KATP channel activator. Neither the protein kinase C modulators nor glyburide produced any effect on coronary flow and left ventricular contractility, when the hearts were prepared from animals either maintained on a cholesterol (1.5%)-enriched diet or treated with lovastatin (5 mg/kg/day per os). Treatment with farnesol (1 mg/kg twice a day for 7 days intravenously) restored the reactivity of hearts from either hypercholesterolaemic or lovastatin-treated animals to protein kinase C modulators. We conclude that non-cholesterol mevalonate products are necessary for the functional integrity of the protein kinase C-KATP channel pathway in the rabbit heart.

L1 ANSWER 9 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:275564 BIOSIS
DN PREV200100275564
TI Role of calcium in the mechanism underlying the inhibitory effect of streptomycin on carotid sinus baroreflex in rats.
AU Qin Xiao-Mei; He Rui-Rong (1)
CS (1) Department of Physiology, Institute of Basic Medicine, Hebei Medical University, Shijiazhuang, 050017: syho@263.net China
SO Shengli Xuebao, (December, 2000) Vol. 52, No. 6, pp. 463-467. print.
ISSN: 0371-0874.
DT Article
LA Chinese
SL Chinese; English
AB The effect of streptomycin (SM) on carotid baroreflex was examined in 23 anesthetized rats with isolated carotid sinus perfusion. The results obtained are as follows. (1) In response to perfusion with SM (200 mumol/L), the functional curve of carotid baroreflex was shifted to the right and upward with a decrease of peak slope (PS) and a reflex decrease in mean arterial pressure (RD) ($P < 0.01$), indicating an inhibitory effect of SM on carotid sinus baroreflex. (2) By perfusing the isolated carotid sinus with high Ca2+ solution (4 mmol/L), the inhibitory effect of SM on carotid baroreflex was partially eliminated. The functional curve of SM was shifted to the left and downward with PS increasing from 0.27 +- 0.04 kPa to 0.37 +- 0.02 kPa ($P < 0.01$) and RD was enhanced from 4.32 +- 0.14 kPa to 6.18 +- 0.17 kPa ($P < 0.01$). On the other hand, the threshold pressure (TP) and saturation pressure (SP) were significantly decreased from 10.29 +- 0.29 kPa to 9.98 +- 0.33 kPa ($P < 0.05$) and from 27.26 +- 0.42 kPa to 25.22 +- 0.38 kPa ($P < 0.05$), respectively. (3) By pretreatment with Bay K 8644 (500 nmol/L), an agonist of calcium channels, the effect of SM on carotid baroreflex was completely abolished. (4) Exposure of the carotid sinus to SM following pretreatment with charybdotoxin (ChTX, 100 nmol/L), a blocker of the Ca2+ -activated K+ channel (KCa), still inhibited the baroreflex. These results suggest that the inhibitory action of SM on carotid baroreflex may be mediated by suppressing Ca2+ influx.

L1 ANSWER 10 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:175582 BIOSIS
DN PREV200100175582
TI An investigation of a putative BKCa ***potassium*** ***channel*** ***activator*** using isolated rat bladder and single cell studies.
AU Williamson, I. J. R. (1); Nunn, P. A. (1); Newgreen, D. T. (1)
CS (1) Department of Discovery Biology, Pfizer Global Research and Development, Sandwich, Kent, CT13 9NJ UK
SO British Journal of Pharmacology, (December, 2000) Vol. 131, No. Proceedings Supplement December, pp. 195P. print.
Meeting Info.: Meeting of the British Pharmacological Society Bradford, England, UK September 06-08, 2000 British Pharmacological Society
. ISSN: 0007-1188.
DT Conference
LA English
SL English

L1 ANSWER 11 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:155161 BIOSIS
DN PREV200100155161
TI Nicorandil can induce severe oral ulceration.
AU Scully, Crispian (1); Azul, Antonio Mano; Crighton, Alexander; Felix, David; Field, Anne; Porter, Stephen R.
CS (1) Eastman Dental Institute of Oral Health Care Sciences, University College London, University of London, 256, Gray's Inn Rd, London, WC1 8LD: www.eastman.ucl.ac.uk, CScully@eastman.ucl.ac.uk UK
SO Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics, (February, 2001) Vol. 91, No. 2, pp. 189-193. print.
ISSN: 1079-2104.
DT Article
LA English
SL English
AB Objective: To increase physicians' and dentists' awareness that nicorandil is a potential inducer of severe mouth ulceration. Study design: Nine new cases of ulceration from 3 European countries were included in this study. Results: Oral ulceration developed within 9 months of beginning nicorandil therapy, and ulcers resolved within 1 month of withdrawal of the drug. No lesions developed on other epithelia. Conclusions: A number of drugs used in the care of patients with cardiovascular disease can cause oral adverse effects. Nicorandil, a new ***potassium*** - ***channel*** ***activator*** used in some countries to treat angina pectoris, precipitates persistent ulcerative stomatitis in some patients.

L1 ANSWER 12 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:71517 BIOSIS
DN PREV200100071517
TI Inhibition of imidazoline I2 site binding by potassium channel modulators.
AU Slattery, D. A. (1); Hudson, A. L. (1); Nutt, D. J. (1)
CS (1) Psychopharmacology Unit, University of Bristol, Bristol, BS8 1TD UK
SO British Journal of Pharmacology, (October, 2000) Vol. 131, No. Proceedings Supplement, pp. 39P. print.
Meeting Info.: Meeting of the British Pharmacological Society Cardiff, Wales, UK July 12-14, 2000 British Pharmacological Society
. ISSN: 0007-1188.
DT Conference
LA English
SL English

L1 ANSWER 13 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:33321 BIOSIS
DN PREV200100033321
TI Inhibitory mechanism of pinacidil on catecholamine secretion from the rat perfused adrenal gland evoked by cholinergic stimulation and membrane depolarization.
AU Lim, Dong-Yoon (1); Park, Geun-Hong; Park, Sang-Hak
CS (1) Department of Pharmacology, College of Medicine, Chosun University, Kwang Ju, 501-759 South Korea
SO Journal of Autonomic Pharmacology, (April, 2000) Vol. 20, No. 2, pp. 123-132. print.
ISSN: 0144-1795.
DT Article
LA English
SL English
AB 1 The present study attempted to investigate the effect of potassium channel openers on secretion of catecholamines (CA) evoked by cholinergic stimulation and membrane depolarization from rat isolated perfused adrenal gland. 2 The perfusion of pinacidil (30-300 muM) into an adrenal vein for 20 min produced dose-dependent inhibition of CA secretion evoked by acetylcholine (ACh; 5.32 mM), high K+ (56 mM), 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP; 100 muM for 2 min), 3-(m-chloro-phenyl-carbamoyl-oxy)-2-butynyl trimethyl ammonium chloride (McN-A-343; 100 muM for 2 min), cyclopiazonic acid (CPA; 10 muM for 4 min) and methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate (Bay-K-8644; 10 muM for 4 min). 3 In the presence of minoxidil (100 muM), which is also known to be a ***potassium*** ***channel*** ***activator*** , CA secretory responses evoked by ACh, high potassium, DMPP, McN-A-343, Bay-K-8644 and CPA were also significantly depressed. 4 In adrenal glands preloaded with pinacidil (100 muM) in the presence of glibenclamide (GB; 1 muM), a specific blocker of ATP-regulated potassium channels, CA secretory responses evoked by ACh, high potassium, DMPP, McN-A-343, Bay-K-8644 and CPA were restored to a considerable extent of the control release as compared with that of pinacidil only. 5 These results suggest that pinacidil causes marked inhibition of CA secretion evoked by stimulation of cholinergic (both nicotinic and muscarinic) receptors, as well as by membrane depolarization, indicating that this effect may be mediated by inhibiting influx of extracellular calcium and release of intracellular calcium in the rat adrenomedullary chromaffin cells. Furthermore, these findings suggest that these potassium channel opener-sensitive membrane potassium channels also play a modulatory role in regulating CA secretion.

L1 ANSWER 14 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:512561 BIOSIS
DN PREV200000512561
TI Calcium gated ***potassium*** ***channel*** ***activator*** , dehydroepiandrosterone sulfate, reduces hypoxic pulmonary hypertension in rats.
AU Bibova, J. (1); Herget, J. (1); Hampl, V. (1)
CS (1) Department of Physiology, Second Medical School, Charles University, Prague Czech Republic
SO Physiological Research, (2000) Vol. 49, No. 4, pp. P7. print.
Meeting Info.: Proceedings of Czech and Slovak Physiological Societies Hradec Kralove, Czechoslovakia February 02-04, 2000
ISSN: 0862-8408.
DT Conference
LA English
SL English

L1 ANSWER 15 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:397289 BIOSIS
DN PREV200000397289
TI Novel potassium channel activators. II. Synthesis and pharmacological

evaluation of 3,4-dihydro-2H-1,4-benzoxazine derivatives: Modification of the aromatic part.
AU Matsumoto, Yuzo (1); Tsuzuki, Ryuji; Matsuhisa, Akira; Masuda, Noriyuki; Yamagiwa, Yoko; Yanagisawa, Isao; Shibanuma, Tadao; Nohira, Hiroyuki
CS (1) Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21, Miyukigaoka, Tsukuba, Ibaraki, 305-8585 Japan
SO Chemical & Pharmaceutical Bulletin (Tokyo), (July, 1999) Vol. 47, No. 7, pp. 971-979. print.
ISSN: 0009-2363.
DT Article
LA English
SL English
AB Three new series of analogues related to 3,4-dihydro-2H-1,4-benzoxazine derivative Ia were synthesized and evaluated for their potassium channel activating activity. In the first series I, where the 6,7-positions were disubstituted, it was found that an electron-withdrawing substituent was preferable at the 6 position, but either an electron-withdrawing or releasing substituent without bulkiness was tolerated at the 7 position. In the second series II, where several heterocycles were introduced into the 6,7-positions, the oxadiazole derivative 6 showed more potent activity than cromakalim. In the third series III, where the benzene ring was replaced by a pyridine ring, borane complex 16 had equivalent activity to cromakalim. Especially, compound 6 showed a potent hypotensive effect with a long duration of action in the spontaneous hypertensive rat and had a lesser increasing effect on intracranial pressure in dogs than 1a and levcromakalim, showing a good profile as an antihypertensiveagent.

L1 ANSWER 16 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:391469 BIOSIS
DN PREV200000391469
TI Buccal ulcerations induced by nicorandil: Prevalence and clinicopathologic study.
AU Marquart-Elbaz, C.; Lipsker, D.; Grosshans, E.; Cribier, B. (1)
CS (1) Clinique Dermatologique (Pr. GROSSHANS) des Hopitaux Universitaires de
Strasbourg, 1, Place de l'Hopital, 67091, Strasbourg Cedex France
SO Annales de Dermatologie et de Venereologie, (Sept., 1999) Vol. 126, No. 8-9, pp. 587-590. print.
ISSN: 0151-9638.
DT Article
LA French
SL English; French
AB Introduction: The first observations of "geant buccal aphtosis" induced by nicorandil were published in 1996. Nicorandil is a ***potassium*** ***channel*** ***activator*** used in the treatment of angina pectoris, which seems to induce specific buccal ulcerations. The purpose of this study was to analyze the clinicopathologic data of patients with aphtosis induced by nicorandil and to study the prevalence of this side effect. Patients and methods: We have seen 3 patients who spontaneously consulted, and 5 patients who were adressed to us after a telephone survey. We have then examined 100 consecutive patients treated by nicorandil for at least 1 month, who were hospitalized in 3 departments of cardiology in Strasbourg, and 100 age -and sex- matched controls who were treated by other antianginal drugs. Results: Our 8 patients suffered from large, chronic and painful ulcerations of a 4-week duration, located on the tongue, the gingiva and the cheeks despite various symptomatic treatments. In one case, histopathologic data were consistent with an eosinophilic ulcer. Prospective study: among 100 patients treated by nicorandil, 5 had unusual chronic buccal ulcerations, whereas none of the 100 controls had aphtosis (p = 0,03). The confidence interval (99 p. 100) of this side effect prevalence was therefore 1 p. 100 to 14 p. 100. Discussion: Nicorandil can induce large and painful buccal ulcerations with severe dysphagia, weight loss, and depression. Dermatologists should be awared of this particuliar side-effect, since our study showed a high prevalence, and because lesions heal rapidly after withdrawal of nicorandil. Why nicorandil may be associated with mouth ulcers remains unanswered. A past history of aphtae could be a cofactor of this side-effect.

L1 ANSWER 17 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:303918 BIOSIS
DN PREV200000303918
TI Developmental changes in pial arteriolar vasodilation to the KATP channel activator pinacidil in fetal sheep.
AU Watanabe, Y.; Traystman, R. J.; Koehler, R. C.
SO FASEB Journal, (March 15, 2000) Vol. 14, No. 4, pp. A428. print.
Meeting Info.: Annual Meeting of Professional Research Scientists: Experimental Biology 2000 San Diego, California, USA April 15-18, 2000 Federation of American Societies for Experimental Biology
. ISSN: 0892-6638.
DT Conference
LA English
SL English

L1 ANSWER 18 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:296818 BIOSIS
DN PREV200000296818
TI Dual regulation of leptin secretion: Intracellular energy and calcium dependence of regulated pathway.
AU Levy, James R.; Gyarmati, Judit; Lesko, John M.; Adler, Robert A.; Stevens, Wayne
SO American Journal of Physiology, (May, 2000) Vol. 278, No. 5 part 1, pp. E892-E901. print.
ISSN: 0002-9513.
DT Article
LA English
SL English
AB Rodent leptin is secreted by adipocytes and acutely regulates appetite and chronically regulates body weight. Mechanisms for leptin secretion in cultured adipocytes were investigated. Acutely, energy-producing substrates stimulated leptin secretion about twofold. Biologically inert carbohydrates failed to stimulate leptin secretion, and depletion of intracellular energy inhibited leptin release. There appears to be a correlation between intracellular ATP concentration and the rate of leptin secretion. Insulin increased leptin secretion by an additional 25%. Acute leptin secretion is calcium dependent. When incubated in the absence of calcium or in the presence of intracellular calcium chelators, glucose plus insulin failed to stimulate leptin secretion. In contrast, basal leptin secretion is secreted spontaneously and is calcium independent. Adipocytes from fatter animals secrete more leptin, even in the absence of calcium, compared with cells from thinner animals. Acute stimulus-secretion coupling mechanisms were then investigated. The ***potassium*** ***channel*** ***activator*** diazoxide and the nonspecific calcium channel blockers nickel and cadmium inhibited acute leptin secretion. These studies demonstrate that intracellular energy production is important for acute leptin secretion and that potassium and calcium flux may play roles in coupling intracellular energy production to leptin secretion.

L1 ANSWER 19 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:272860 BIOSIS
DN PREV200000272860
TI Effect of nicorandil upon different guinea-pig and rat isolated organ preparations in vitro.
AU Barcenilla, Alberto; Alamo, Cecilio (1); Carvajal, Alfonso; Garcia-Pozo, Javier; Velasco, Alfonso
CS (1) Departamento de Farmacologia, Facultad de Medicina, Universidad de Alcala, Ctra. Madrid-Barcelona km 33,600, Campus Universitario, E-28871, Madrid Spain
SO Arzneimittel-Forschung, (April, 2000) Vol. 50, No. 4, pp. 341-344. print.
ISSN: 0004-4172.
DT Article
LA English
SL English; German
AB A study of the effect of nicorandil (N-2-(hydroxyethyl)nicotinamide nitrate, CAS 65141-46-0), a potassium channel and guanylatecyclase activator, upon preparations of rat vas deferens and uterus, and guinea pig ileum was performed. Nicorandil does not modify rat isolated vas deferens responses to noradrenaline (norepinephrine) and potassium. The drug exerts a non-competitive antagonist effect upon rat isolated uterus response to serotonin, histamine, oxytocin, and, at high concentrations, inhibits guinea-pig isolated ileum responses to acetylcholine, histamine, 4-aminopyridine and potassium.

L1 ANSWER 20 OF 566 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:253218 BIOSIS
DN PREV200000253218
TI Novel potassium channel activators. III. Synthesis and pharmacological evaluation of 3,4-dihydro-2H-1,4-benzoxazine derivatives: Modification at the 2 position.
AU Matsumoto, Yuzo (1); Uchida, Wataru; Nakahara, Hideaki; Yanagisawa, Isao; Shibanuma, Tadao; Nohira, Hiroyuki
CS (1) Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21, Miyukigaoka, Tsukuba, Ibaraki, 305-8585 Japan
SO Chemical & Pharmaceutical Bulletin (Tokyo), (March, 2000) Vol. 48, No. 3, pp. 428-432. print.
ISSN: 0009-2363.
DT Article
LA English
SL English
AB A new series of 3,4-dihydro-2H-1,4-benzoxazine derivatives, where various substituents were introduced into one of the geminal dimethyl groups at the 2 position, were synthesized and their potassium channel-activating activity was evaluated. Introduction of a hydroxyl group, as in compound 5, resulted in good solubility in water and a long duration of action compared with the parent compound 1. Introduction of a nitrato group, as in compound 8, produced typical nitrate activity such as exhibited by nitroglycerine in addition to potassium channel-activating activity. X-ray structural analysis of compound 5 showed that the sum of the bond angles around the N atom at the 4 position was 357.8degree, suggesting that the N atom had an approximately sp2-like planar bond configuration.

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL
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FILE 'CAPLUS' ENTERED AT 11:15:06 ON 14 NOV 2001

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FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 10:58:25 ON 14 NOV 2001
L1 566 S POTASSIUM CHANNEL ACTIVATOR
L2 29 S PERMEABILITY AND BRAIN AND DELIVER
L3 0 S L1 AND L2
L4 0 S L1 AND PERMEABLILITY
L5 6 S L1 AND PERMEABILITY
L6 6 DUP REM L5 (0 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 11:07:08 ON 14 NOV 2001

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:10:47 ON 14 NOV 2001

FILE 'STNGUIDE' ENTERED AT 11:10:54 ON 14 NOV 2001

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:15:06 ON 14 NOV 2001

=> s l1 and brain
L7 35 L1 AND BRAIN

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 26 DUP REM L7 (9 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 26 ANSWERS - CONTINUE? Y/(N):y

L8 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 2001:564889 CAPLUS
DN 135:132471
TI Method using potassium channel agonists for delivering a medicant to an abnormal ***brain*** region and/or a malignant tumor
IN Black, Keith L.; Ningaraj, Nagendra S.
PA Cedars-Sinai Medical Center, USA
SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001054771	A2	20010802	WO 2001-US2743	20010126

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-491500 A 20000126
US 2000-615854 A 20000714
AB Methods are disclosed for selectively delivering a medicant to an abnormal ***brain*** region and/or to a malignant tumor in a mammalian subject, including a human. A medicant is administered simultaneously or substantially simultaneously with a calcium- or ATP-dependent potassium channel [KCa or KATP] activator (other than bradykinin or a bradykinin analog), such as a direct potassium channel agonist or an indirect ***potassium*** ***channel*** ***activator*** , such as an activator of sol. guanylyl cyclase (e.g., nitric oxide or a nitric oxide donor) or an activator of cyclic GMP-dependent protein kinase, whereby the medicant is delivered selectively to the cells of the abnormal ***brain*** region and/or to the tumor, compared to normal tissues. Thus, among the disclosures is a method of treating a malignant tumor in a human subject. Also disclosed are pharmaceutical compns. that combine a ***potassium*** ***channel*** ***activator*** together with a medicant and a kit for enhancing the delivery of a medicant to an abnormal ***brain*** region and/or to a malignant tumor.

L8 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 2001:564822 CAPLUS
DN 135:132469
TI Method for using potassium channel activation for delivering a medicant to an abnormal ***brain*** region and/or a malignant tumor
IN Black, Keith L.; Ningaraj, Nagendra S.
PA Cedars-Sinai Medical Center, USA
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001054680	A2	20010802	WO 2001-US2742	20010126

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-491500 A 20000126
US 2000-615854 A 20000714
AB Disclosed are methods of selectively delivering a medicant to an abnormal ***brain*** region and/or to a malignant tumor in a mammalian subject, including a human. A medicant is administered simultaneously or substantially simultaneously with a calcium- or ATP-dependent potassium channel [KCa or KATP] activator (other than bradykinin or a bradykinin analog), such as a direct potassium channel agonist or an indirect ***potassium*** ***channel*** ***activator*** , such as an activator of sol. guanylyl cyclase (e.g., nitric oxide or a nitric oxide donor) or an activator of cGMP-dependent protein kinase, whereby the medicant is delivered selectively to the cells of the abnormal ***brain*** region and/or to the tumor, compared to normal tissues. Thus, among the disclosures is a method of treating a malignant tumor in a human subject. Also disclosed are pharmaceutical compns. that combine a ***potassium*** ***channel*** ***activator*** together with a medicant and a kit for enhancing the delivery of a medicant to an abnormal ***brain*** region and/or to a malignant tumor.

L8 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 2001:31352 CAPLUS
DN 134:99581
TI Method and composition for inhibition of vasospasm
IN Tamargo, Rafael J.
PA Johns Hopkins University, USA
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001002009	A1	20010111	WO 2000-US18323	20000630

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-142643 P 19990706
AB A method for inhibiting cerebral vasospasm in a mammal is provided, wherein the mammal is administered an amt. of an anti-CD11/CD18 antibody sufficient to inhibit onset or progression of vasospasm in the mammal. The method further comprises administration of vasodilator, anti-inflammatory, calcium antagonist, immunosuppressant, ***potassium*** ***channel*** ***activator*** , PAF inhibitor, neuropeptide Y receptor inhibitor, complement-depleting substance, haptoglobin-contg. substance, and substance interfering leukocyte adhesion to or filtration of endothelial tissue.
RE.CNT 4
RE
(1) Bavbek; Stroke 1998, V29, P1930 CAPLUS
(2) Handa; Acta Neurochir (Wien) 1995, V132, P92 MEDLINE
(3) Oshiro; Stroke 1997, V28, P2031 CAPLUS
(4) Wright; US 5147637 A 1992 CAPLUS

L8 ANSWER 4 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:509497 BIOSIS
DN PREV200100509497
TI Diazoxide, but not cyclosporin A or hypothermia, preserves N-methyl-D-aspartate (NMDA)-induced cerebral dilation after ischemia in piglets.
AU Busija, D. W. (1); Perciaccante, J. (1); Domoki, F. (1)
CS (1) Physiology/Pharmacology, Wake Forest Univ. School of Medicine, Winston-Salem, NC USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 887. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DT Conference
LA English
SL English

AB We have previously shown that diazoxide, a specific activator of mitochondrial ATP-sensitive potassium channels (mKATP), preserves vascular dilator responses to application of NMDA after ischemia (Stroke 30:2713-2718, 1999). We also have shown that diazoxide administration limits infarct volume in neonatal and adult rats following cerebral ischemia. In addition, other interventions that affect mitochrondial function, such as cyclosporin A (CsA) administration and ***brain*** cooling, also reduce infarct size after ischemia. Thus, we assessed whether CsA and hypothermia were as effective as diazoxide in protecting neuronal function against ischemia. We examined effects of NMDA in anesthetized piglets on pial arteriolar diameter before ischemia and 1 hour after 10 min of global ischemia in three groups: diazoxide pretreated (10-5M; n=5), CsA pretreated (10-4M; n=6), and local ***brain*** cooling (34degreeC; n=11). Total ***brain*** ischemia was induced by increasing intracranial pressure. In the diazoxide group, arterioles (baseline diameterapprx100 microns) dilated by 15+-9% versus 14+-5% at 5X10-5M NMDA (ns) and by 41+-13% versus 39+-8% at 10-4M NMDA (ns), before and after ischemia, respectively. In the CsA group, arteriolar dilation was reduced (p<.05) by ischemia to 6+-4% at 5X10-5M NMDA and 13+-8% at 10-4M NMDA. In the hypothermia group, dilation was reduced to 8+-5% at 5X10-5M NMDA and 20+-5% at 10-4M NMDA after ischemia (p<.05). We conclude that diazoxide has specific neuroprotective effects via KATP on neuronal function in the early post-ischemic period.

L8 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 2000:814310 CAPLUS
DN 133:359255
TI Nitrosated and nitrosylated potassium channel activators, compositions, and methods of use
IN Garvey, David S.; Saenz De Tejada, Inigo
PA Nitromed, Inc., USA
SO PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000067754	A1	20001116	WO 2000-US12957	20000512

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-133888 P 19990512
OS MARPAT 133:359255
AB The invention describes nitrosated and/or nitrosylated potassium channel activators, as well as comprns. comprising at least one nitrosated and/or nitrosylated ***potassium*** ***channel*** ***activator*** and, optionally, at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide, or is a substrate for nitric oxide synthase, and/or at least one vasoactive agent. The invention also provides comprns. comprising at least one ***potassium*** ***channel*** ***activator*** and at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide, or is a substrate for nitric oxide synthase, and/or at least one vasoactive agent. The invention further provides methods for treating or preventing sexual dysfunction in males and females, for enhancing sexual response in males and females, and for treating or preventing cardiovascular disorders, cerebrovascular disorders, hypertension, asthma, baldness, urinary incontinence, epilepsy, sleep disorders, gastrointestinal disorders, migraines, irritable bowel syndrome, and sensitive skin.
RE.CNT 5
RE
(1) Anon; Bioorg Med Chem Lett 1997, V7(24), P3095 CAPLUS
(2) Anon; J Pharmacol Exp Ther 1984, V229(3), P793 CAPLUS
(3) Casselia Ag; DE 4420523 A1 1995 CAPLUS
(4) Chugai Seiyaku K K; DE 2714713 A1 1977 CAPLUS
(5) Yissum Research Development Company Of The Hebrew University Of Jerusalem; WO 9842661 A1 1998 CAPLUS

L8 ANSWER 6 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:71517 BIOSIS
DN PREV200100071517
TI Inhibition of imidazoline I2 site binding by potassium channel modulators.
AU Slattery, D. A. (1); Hudson, A. L. (1); Nutt, D. J. (1)
CS (1) Psychopharmacology Unit, University of Bristol, Bristol, BS8 1TD UK
SO British Journal of Pharmacology, (October, 2000) Vol. 131, No. Proceedings Supplement, pp. 39P. print.
Meeting Info.: Meeting of the British Pharmacological Society Cardiff, Wales, UK July 12-14, 2000 British Pharmacological Society
. ISSN: 0007-1188.
DT Conference
LA English
SL English

L8 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1999:402731 CAPLUS
DN 131:223269
TI Attenuation of basilar artery spasm after experimental subarachnoid hemorrhage in rabbit by ***potassium*** ***channel*** ***activator*** cromakalim
AU Kwan, Aij-Lie; Lin, Chih-Lung; Howng, Shen-Long
CS Department of Neurosurgery, Kaohsiung Medical College Hospital, Kaohsiung, 807, Taiwan
SO Kaohsiung J. Med. Sci. (1999), 15(5), 268-273
CODEN: KJMSFM; ISSN: 0257-5655
PB Kaohsiung Journal of Medical Sciences
DT Journal
LA English
AB Cerebral vasospasm assocd. with aneurysmal subarachnoid hemorrhage (SAH) remains a major complication in patients suffering from SAH. Regulation of membrane potential of arterial smooth muscle through activation or inhibition of potassium (K+) channel activity provides an important mechanism to dilate or constrict arteries. The present study examd. the effect of a K+ channel activator, cromakalim, on cerebral vasospasm following exptl. SAH. By the route of topical application and intra-arterial injection, basilar arteries were exposed transclivally and measured online using videomicroscopic camera. Continuous microinjection from right vertebral artery was given after the result of application was obsd. Basilar artery spasm induced by SAH was released by topical or intra-arterial administration of cromakalim, and this beneficial effect against cerebral vasospasm was dose-dependent. There was no significant difference between topical and intra-arterial administration of cromakalim. These results indicate that K+ channel activator may play an important role for ameliorating cerebral vasospasm. An important goal of future studies will be to carefully evaluate the possibility and effect of intra-arterial administration of cromakalim to treat angiog. vasospasm.
RE.CNT 24
RE
(1) Asano, M; Eur J Pharmacol 1994, V263, P121 CAPLUS
(2) Asano, M; J Auton Nerv Syst 1994, V49, PS151 CAPLUS
(4) Fulton, D; Br J Pharmacol 1994, V113, P954 CAPLUS
(6) Ishizaka, H; Circ Res 1996, V78, P50 CAPLUS
(8) Ksoll, E; Naunyu Schmiedebergs Arch Pharmacol 1991, V343, P377 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998053231 EMBASE
TI Systemic administration of the ***potassium*** ***channel*** ***activator*** cromakalim attenuates cerebral vasospasm after experimental subarachnoid hemorrhage.
AU Kwan A.-L.; Lin C.-L.; Yanamoto H.; Howng S.-L.; Kassell N.F.; Lee K.S.; Solomon R.A.; Dacey R.G. Jr.; Macdonald R.L.; Megyesi J.F.; Findlay J.M.; Hodge C.J. Jr.
CS Dr. K.S. Lee, Box 420 HSC, Department of Neurological Surgery, University of Virginia, Charlottesville, VA 22908, United States
SO Neurosurgery, (1998) 42/2 (347-351).
Refs: 28
ISSN: 0148-396X CODEN: NRSRDY
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English
AB OBJECTIVE: Cerebral vasospasm is a primary complication after aneurysmal subarachnoid hemorrhage (SAH). Recent evidence indicates that the activation of potassium (K+) channels may be of benefit in relieving spastic constriction. The present study examined the effects of systemic administration of a K+ channel activator, cromakalim, on cerebral vasospasm after experimental SAH. METHODS: Experimental SAH was performed in rabbits by injecting autologous blood into the cisterna magna. Intravenous injections of cromakalim or vehicle were administered twice daily with the first injection administered 1 hour after induction of SAH. Animals were killed by perfusion- fixation 48 hours after SAH. Basilar arteries were removed and sectioned, and the luminal cross-sectional areas were measured. RESULTS: Experimental SAH induced cerebral vasospasm in untreated and vehicle-treated animals. Cromakalim attenuated cerebral vasospasm in a dose-dependent manner. This effect achieved statistical significance at doses of 0.1 and 0.3 mg/kg. CONCLUSION: These results support the concept that targeting vascular K+ channels can be of benefit in preventing the development of cerebral vasospasm. The findings also indicate that cromakalim represents a potential therapeutic agent for the treatment of cerebrovascular pathophysiology after SAH.

L8 ANSWER 9 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97307770 EMBASE
DN 1997307770
TI An ATP-sensitive ***potassium*** ***channel*** ***activator*** reduces infarct volume in focal cerebral ischemia in rats.
AU Takaba H.; Nagao T.; Yao H.; Kitazono T.; Ibayashi S.; Fujishima M.
CS H. Takaba, Second Dept. of Internal Medicine, Faculty of Medicine, Kyushu

Univ., Maidashi 3-1-1, Higashi-ku, Fukuoka 812-82, Japan
SO American Journal of Physiology - Regulatory Integrative and Comparative Physiology, (1997) 273/2 42-2 (R583-R586).
Refs: 23
ISSN: 0363-6119 CODEN: AJPRDO
CY United States
DT Journal; Article
FS 002 Physiology
LA English
SL English
AB ATP-sensitive potassium channels are activated under hypoxic or ischemic conditions. The effects of ATP-sensitive potassium channel activators on cerebrovasculature and cerebral blood flow (CBF) are not well understood. We examined the effect of the ATP-sensitive ***potassium*** ***channel*** ***activator*** Y-26763 on focal cerebral ischemia in rats. In 24 spontaneously hypertensive rats, either Y-26763 (24 .mu.g/kg) or vehicle was given by intracarotid infusion over 60 min, starting 30 min before photochemically induced thrombotic occlusion of the middle cerebral artery. CBF was measured by laser-Doppler flowmetry in the peri-ischemic penumbral cortex. Although Y-26763 lowered systemic blood pressure by 13 mmHg, the infarct volume assessed 3 days after the occlusion was significantly smaller in the Y-26763-treated group (n = 12, 71.2 .+-. 22.0 mm8) than in the control group (.eta. = 12, 94.7 .+-. 20.4 mm3, P = 0.013). Y- 26763 did not affect CBF before or after occlusion compared with CBF values of the control group. The results are consistent with the view that the activation of the ATP-sensitive potassium channel is neuroprotective in focal cerebral ischemia.

L8 ANSWER 10 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AN 1997:77799 BIOSIS
DN PREV199799384502
TI The effect of the ***potassium*** ***channel*** ***activator*** , cromakalim, on antidepressant drugs in the forced swimming test in mice.
AU Redrobe, J. P.; Pinot, P.; Bourin, M. (1)
CS (1) Dep. Pharmacol., GIS Medicament, 1 rue Gaston Veil, 44035 Nantes cedex
France
SO Fundamental & Clinical Pharmacology, (1996) Vol. 10, No. 6, pp. 524-528.
ISSN: 0767-3981.
DT Article
LA English
AB The forced swimming test (FST) is a widely used behavioural model to predict potential antidepressant (AD) action of compounds in humans. It has been previously shown that pretreatment with lithium, quinine and clonidine had additive effects on AD drugs in the FST, an effect proposed to be a result of potassium channel blockade. It is possible that pretreatment with potassium channel openers may induce opposite effects to those seen following pretreatment with potassium channel blockers in the FST. Pretreatment with cromakalim (CROM) (1 mg/kg, intraperitoneally (ip)) antagonized the anti-immobility effects of the mixed noradrenaline (NA)/5-hydroxytryptamine (5-HT)reuptake inhibitors imipramine and amitriptyline (P lt 0.05). CROM administration (0.06 and 1 mg/kg, ip) also blocked the AD-like effects of the specific NA reuptake inhibitor, desipramine, and the selective serotonin reuptake inhibitor, paroxetine (P lt 0.05 and P lt 0.01, respectively). Pretreatment with CROM via gavage (1 mg/kg) antagonized the AD-like effects of imipramine, amitriptyline, desipramine and paroxetine. CROM treatment (via ip route or gavage) did not have any significant effect on the anti-immobility activity of the atypical AD mianserin at any of the doses employed. Another potassium-channel opener, minoxidil (MINOX), which does not cross the blood- ***brain*** barrier, was also tested to eliminate the possibility that CROM may be acting via peripheral/local mechanisms. MINOX (32 mg/kg) failed to antagonize anti-immobility effects of any of the AD tested. In conclusion, the results of the present study suggest that CROM is only acting on drugs involved with neurotransmitter uptake inhibition.

L8 ANSWER 11 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AN 1996:466397 BIOSIS
DN PREV199699188753
TI Electrophysiological investigation of adenosine trisphosphate-sensitive potassium channels in the rat substantia nigra pars reticulata.
AU Stanford, I. M.; Lacey, M. G. (1)
CS (1) Dep. Pharmacology, Med. Sch., Univ. Birmingham, Edgbaston, Birmingham
B15 2TT UK
SO Neuroscience, (1996) Vol. 74, No. 2, pp. 499-509.
ISSN: 0306-4522.
DT Article
LA English
AB Adenosine trisphosphate-sensitive potassium (K-ATP) channels in the substantia nigra pars reticulata were studied in rat ***brain*** slices using whole-cell patch clamp recording. Substantia nigra pars reticulata neurons were identified as such by their spontaneous action potential firing at mean rate of 15.3 Hz, virtual absence of hyperpolarization-activated inward current I-h, and unresponsiveness to dopamine (30 mu-M), quinpirole (10 mu-M) and (Met)enkephalin (10 mu-M). Intracellular dialysis with Mg-2+-ATP-free pipette solutions caused a slowly developing membrane hyperpolarization (13 +- 4 mV), accompanied by a cessation of action potential firing, or an outward current (79 +- 30 pA at around -60 mV), which were reversed by the sulphonylurea K-ATP channel blockers tolbutamide (100 mu-M) and glibenclamide (3 mu-M). When Mg-2+-ATP
(2 mM) was included in the recording pipette no membrane hyperpolarization or outward current was observed. Neither the sulphonylureas nor the ***potassium*** ***channel*** ***activator*** lemakalim (200 mu-M) altered membrane potential, firing rate or holding current under these recording conditions. The outward current induced by dialysis with Mg-2+-ATP-free solutions reversed polarity negative to -94 +- 9 mV (9 cells), close to the estimated K+ equilibrium potential (-105 mV) for the conditions used, and was associated with a conductance increase that was blocked by Ba-2+ (100 mu-M). The current blocked by the sulphonylureas had a similar reversal potential (-97 +- 7 mV; 13 cells), and both currents were voltage independent over the range -50 to -100 mV with slope conductance of approximately 2.0 nS. Outward synaptic currents were evoked by single shock electrical stimulation, in the presence of glutamate receptor antagonists, at a holding potential of -50 mV. These synaptic currents were blocked by bicuculline (10 mu-M) and reversed polarity at around - 65 mV, close to the Cl- equilibrium potential, and were thus mediated by GABA-A receptors. They were reversibly depressed by 37 +- 14% in lemakalim (200 mu-M) in 6/12 cells tested, an effect that was partially reversed by tolbutamide (200 mu-M). It is concluded that functional K-ATP channels are present both presynaptically and postsynaptically in the substantia nigra pars reticulata. Postsynaptic K-ATP channels may control excitability in conditions where intracellular ATP is reduced, whereas presynaptic K-ATP channels, sensitive to the ***potassium*** ***channel*** ***activator*** lemakalim, can modulate the release of GABA, which probably arises from fibres of extranigral origin. Pharmacological differences between these two sites could be exploited to treat epilepsies, dyskinesias and akinesia.

L8 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1995:733459 CAPLUS
DN 123:143653
TI Biaryl ureas and related compounds for use as cardiovascular agents.
IN Atwal, Karnail; Ferrara, Francis N.; Ding, Charles Z.
PA USA
SO Can. Pat. Appl., 39 pp.
CODEN: CPXXEB
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CA 2132771	AA	19950408	CA 1994-2132771	19940923
US 5547966	A	19960820	US 1993-134195	19931007
EP 656350	A1	19950607	EP 1994-306813	19940916
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AU 9474463	A1	19950427	AU 1994-74463	19941006
AU 690133	B2	19980423		
JP 07188151	A2	19950725	JP 1994-243895	19941007

PRAI US 1993-134195 19931007
OS MARPAT 123:143653
GI

/ Structure 1 in file .gra /

AB Title compds. I [X = single bond, O, CO, S, NH, or alkylimino; Y = O, S, or NCN; R1 = alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl; R2 = H, alkyl, haloalkyl, alkenyl, alkynyl, cyano, NO2, CHO, CO2H, halo, (un)substituted amino, etc.; R3 = H, alkyl, OH, alkoxy, (un)substituted amino, cyano, NO2; R4 = aryl, aralkyl, heterocyclo, heterocycloalkyl; R5, R5' = H, alkyl, (un)substituted alkylamino, haloalkyl; or R4R5 form ring with 5 to 7 members and optional O, S, or (un)substituted NH] and salts are claimed, along with 18 specific compds. which were also prepd. These compds. have potassium channel activating activity and are useful, e.g., as cardiovascular agents (no data). For example, tert-butylbenzene underwent 2,4-dinitration (70%), redn. of the 4-nitro group to amino (86%), diazotization and cyanation of the group to give a benzonitrile (42%), and redn. of the remaining nitro group with SnCl2 (100%) to give 3-amino-4-(tert-butyl)benzonitrile. Reaction of this with benzyl isocyanate gave title compd. II in 70% yield.

L8 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1995:581892 CAPLUS
DN 123:831
TI Potassium channel activators decrease endogenous glutamate release from rat cerebellar slices
AU Dickie, B. G. M.; Davies, J. A.
CS Dep. Pharmacol. Therapeutics, Univ. Wales Coll. Med., Cardiff, UK
SO Amino Acids (1995), 8(2), 159-69
CODEN: AACIE6; ISSN: 0939-4451
DT Journal
LA English
AB The effects of the sulfonylurea activators of ATP-sensitive potassium channels (K+ATP), cromakalim and pinacidil, on the evoked-release of endogenous glutamate from superfused slices of rat cerebellum was examd. K+-stimulated release was Ca2+-dependent, whereas tetrapentylammonium (TPeA)-evoked release occurred both in the presence and absence of Ca2+, but was significantly greater in Ca2+-free medium. The Ca2+-dependent TPeA and K+-evoked release of glutamate was inhibited by both cromakalim and pinacidil in a concn.-dependent fashion. However, although cromakalim markedly reduced Ca2+-independent TPeA-evoked release, pinacidil was

ineffective. In addn., the vehicle for cromakalim, ethanol, markedly potentiated both Ca2+-dependent and -independent TPeA-evoked release, but not K+-evoked release. Despite a high concn. of sulfonylurea binding sites and a dense glutamatergic innervation, the concns. of K+ATP channel activators required to inhibit stimulus-evoked release from the cerebellum are higher than those reported to inhibit glutamate release or reduce neuronal activity in other parts of the CNS.

L8 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1995:702758 CAPLUS
DN 123:132355
TI Effects of potassium channel activators on isolated cerebral arteries of large and small diameter in the cat
AU Schilling, Lothar; Parsons, Andrew A.; Wahl, Michael
CS Department of Physiology, University of Munich, Munich, Germany
SO J. Neurosurg. (1995), 83(1), 123-8
CODEN: JONSAC; ISSN: 0022-3085
DT Journal
LA English
AB The smooth-muscle relaxant action of ATP-sensitive potassium (KATP) channels in cerebral arteries of large diam. has been confirmed in a no. of in vitro studies, but there is still debate about the presence of KATP channels in small cerebral arteries. In the present study, the authors compare the effects of cromakalim and bimakalim, two putative KATP channel activators, in different parts of the feline isolated middle cerebral artery (MCA) designated proximal, intermediate, and distal. The latter corresponds to those small pial arteries that are usually studied in vivo. In ring segments precontracted with 10-5 M of uridine-5-triphosphate (UTP), both cromakalim and bimakalim induced concn.-related relaxation, with bimakalim being more potent than cromakalim, and no significant differences noted among segments obtained from the different regions of the MCA. In vessels precontracted by adding 30 mM KCl the potency of cromakalim and bimakalim was reduced compared with that obtained after UTP precontraction. In the presence of 10-6 M glibenclamide, an antagonist of KATP channel activators, the concn.-effect curve to bimakalim was shifted to the right in the proximal and distal MCA, indicating a similar route of action for bimakalim and cromakalim in these arteries. The present study therefore indicates the presence of KATP channels in isolated small cerebral arteries according to results obtained in vivo. Activators of KATP channels may prove helpful in the treatment of vasospasm, which may occur in large and small cerebral arteries after subarachnoid hemorrhage.

L8 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1994:541660 CAPLUS
DN 121:141660
TI Potassium channel activators and use thereof in therapy
IN Evans, John Morris; Vong, Kuok Keong; Willette, Robert Nicholas
PA SmithKline Beecham PLC, UK; SmithKline Beecham Corporation
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9413297	A1	19940623	WO 1993-GB2515	19931208
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 674519	A1	19951004	EP 1994-902047	19931208
R: BE, CH, DE, ES, FR, GB, IT, LI, NL				
JP 08504433	T2	19960514	JP 1993-513937	19931208

PRAI GB 1992-25859 19921211
WO 1993-GB2515 19931208
OS MARPAT 121:141660
AB Heterocyclic compds., such as (benzopyranyl)indole derivs. are effective for the treatment and/or prophylaxis of anxiety, mania, depression, the effects assocd. with withdrawal from substances of abuse such as cocaine, nicotine, alc. and benzodiazepines, disorders treatable and/or preventable with anticonvulsive agents, such as epilepsy, cerebral ischemia, disorders resulting from sub-arachnoid hemorrhage, Parkinson's disease, migraine and/or psychosis.

L8 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1994:549100 CAPLUS
DN 121:149100
TI Potassium channel activators for use in therapy for ***brain*** disorders and effects associated with withdrawal from abused substances
IN Vong, Kuok Keong; Evans, John Morris; Nadler, Guy Marguerite Marie Gerard; Willette, Robert Nicholas
PA SmithKline Beecham PLC, UK; SmithKline Beecham Corporation
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9413292	A1	19940623	WO 1993-GB2514	19931208
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 673248	A1	19950927	EP 1994-902046	19931208
R: BE, CH, DE, ES, FR, GB, IT, LI, NL				
JP 08504432	T2	19960514	JP 1993-513938	19931208

PRAI GB 1992-25860 19921211
WO 1993-GB2514 19931208
OS MARPAT 121:149100
AB A method of treatment and/or prophylaxis of anxiety, mania, depression, the effects assocd. with withdrawal from substances of abuse such as cocaine, nicotine, alc. and benzodiazepines; disorders treatable and/or preventable with anticonvulsive agents, such as epilepsy; and in the treatment or prevention of cerebral ischemia, disorders resulting from sub-arachnoid hemorrhage, Parkinson's disease, migraine, and/or psychosis, comprises administering to the sufferer in need thereof an effective or propylactic amt. of a ***potassium*** ***channel*** ***activator*** (Markush included). Trans-3-cyano-5-(4-fluorobenzamido)-6,7,8,9-tetrahydro-5H-benzocycloheptan-6-ol and trans-7-cyano-5-(4-fluorobenzamino)-4-hydroxy-2,2-dimethyl-2,3,4,5-tetrahydro-1-benzoxepine are specifically claimed. Prepn. of selected compds. of the invention are included. Trans-7-(4-fluorobenzamido)-5,6-dihydro-6-hydroxy-2-nitro-5,5-dimethyl-7H-thieno[3,2-b]pyran enhanced the threshold of shock by 95% at 30 mg/kg p.o. in a rodent maximal electroshock seizure threshold test.

L8 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1995:348836 CAPLUS
DN 122:122979
TI Potassium channel activators counteract anoxic hyperexcitability but not 4-aminopyridine-induced epileptiform activity in the rat hippocampal slice
AU Mattia, D.; Nagao, T.; Rogawski, M. A.; Avoli, M.
CS Montreal Neurol. Inst. Dep. Neurol. Neurosurgery, McGill Univ., Montreal, PQ, H3A 2B4, Can.
SO Neuropharmacology (1994), 33(12), 1515-22
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB The K+ channel activators diazoxide and cromakalim were investigated for effects on 4-aminopyridine (4AP)-induced epileptiform activity in adult rat hippocampal slices maintained in vitro. Under normal conditions of oxygenation, 4AP (50 .mu.M) induced two types of field potentials in extracellular recordings from the CA3 stratum radiatum (apical dendritic region): epileptiform interictal discharge-like events occurring at a frequency of 0.75 Hz and long-lasting neg.-going potentials mediated by GABA receptor activation that occurred at 0.03 Hz (slices). Neither diazoxide (0.65-1.3 mM, slices) nor cromakalim (50-200 .mu.M, slices) altered these two types of discharge. Brief periods of anoxia (4-6 min) reduced the frequency of the 4AP-induced interictal-like events (from 0.75 Hz to 0.19 Hz, slices). In 45% of the expts., the depressant effect of anoxia was preceded by a period of hyperexcitability consisting of a transient (36.1 s) increase in the frequency of interictal-like events riding on a neg.-going DC shift (slices). Both responses to anoxia were reversible upon reoxygenation. In contrast, the rate of occurrence of the GABA-mediated potentials was unaffected by the anoxic episodes. Perfusion with cromakalim (slices) or diazoxide (slices) abolished the initial period of hyperexcitability produced by O2 deprivation but did not alter the subsequent depression of activity. The expts. indicate that the K+ channel activators can prevent the initial hyperexcitability produced by anoxia, but do not influence 4AP-induced epileptiform activity in normoxic conditions. These findings suggest that K+ channel opener drugs might be useful in the treatment of seizures occurring in the setting of status epilepticus or cerebrovascular disease.

L8 ANSWER 18 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1994:595365 CAPLUS
DN 121:195365
TI Maturation enhances the sensitivity of ovine cerebral arteries to the ATP-sensitive ***potassium*** ***channel*** ***activator*** lemakalim
AU Pearce, William J.; Elliott, Scott R.
CS Dep. Physiol., Loma Linda Univ. Sch. Med., Loma Linda, CA, 92350, USA
SO Pediatr. Res. (1994), 35(6), 729-32
CODEN: PEREBL; ISSN: 0031-3998
DT Journal
LA English
AB A wide variety of previous studies have demonstrated that arterial reactivity and contractility change dramatically during maturation. In light of recent findings that binding sites for glibenclamide, a ligand for ATP-sensitive potassium (KATP) channels, become more abundant with age in many tissues, the present studies examine the hypothesis that maturational changes in vascular reactivity involve changes in arterial electrophysiol. characteristics. To test this hypothesis, we detd. the dose-response relation to lemakalim, a selective activator of KATP channels, in isolated endothelium-denuded segments of the second (2B, internal diam. .apprxeq. 200 .mu.m) and fourth (4B, internal diam. .apprxeq. 125 .mu.m) branches of middle cerebral arteries taken from newborn (3-7 d old) and adult sheep. At 100 .mu.M, lemakalim completely relaxed serotonin-induced tone in all arteries. However, -log ED50 values were 29 to 43 times greater in adult (2B, 7.15 .+-. 0.38; 4B, 6.61 .+-. 0.42) than in newborn (2B, 5.52 .+-. 0.25; 4B, 5.15 .+-. 0.24) segments. Correspondingly, Hill values were significantly smaller in adults (2B, 0.47 .+-. 0.17; 4B, 0.71 .+-. 0.30) than in newborns (2B, 1.40 .+-. 0.35; 4B, 3.30 .+-. 0.92). These findings demonstrate that KATP channels are less sensitive to activation in newborn than in adult cerebral arteries. Given the important influence of KATP channels on vascular tone, and their possible role in many cardiovascular responses, the present data suggest that maturational increases in the activity of KATP channels contribute significantly to age-related changes in cerebrovascular contractility.

L8 ANSWER 19 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 94274482 EMBASE
DN 1994274482
TI Therapeutic potential of potassium channel activators in coronary heart disease.
AU Haeusler G.; Lues I.
CS Pharmaceutical Research Development, E Merck, Frankfurter Strasse 250,D-6100 Darmstadt, Germany
SO European Heart Journal, (1994) 15/SUPPL. C (82-88).
ISSN: 0195-668X CODEN: EHJODF
CY United Kingdom
DT Journal; General Review
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Potassium channel activators have the ability to open potassium channels in a variety of cells. Since most of their effects are antagonized by antidiabetic sulfonylureas, the ATP-sensitive potassium channel is their likely target. Opening of potassium channels leads to hyperpolarization of the surface membrane with consequent closure of voltage-dependent ion channels and reduction of free intracellular calcium ions. Currently available potassium channel activators including aprikalim, bimakalim, cromakalim, emakalim, nicorandil, pinacidil etc., display a high affinity for potassium channels of vascular smooth muscle. Vasodilation and a reduction in systemic vascular resistance are their prominent pharmacological effects. Coronary and cerebral arteries are highly sensitive to ***potassium*** ***channel*** ***activator*** -induced dilation. Apart from treatment of hypertension potassium channel activators appear to have therapeutic potential in coronary heart disease. They reduce cardiac afterload, increase native and collateral coronary blood flow and reduce the size of experimental myocardial infarcts. This last effect cannot be satisfactorily explained entirely by haemodynamic or coronary vascular actions of potassium channel activators and a cardioprotective effect is postulated. For these drugs ischaemia-induced and activator-induced opening of cardiac ATP-sensitive potassium channels appear to work in concert. Nicorandil combines the pharmacological properties of an organic nitrate with those of potassium channel activators. Experimental and clinical results characterize nicorandil as a unique and promising drug for the treatment of coronary heart disease.

L8 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1993:486044 CAPLUS
DN 119:86044
TI Potassium channel activating compounds and methods of use thereof
IN Cherksey, Bruce
PA New York University, USA
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9308800	A1	19930513	WO 1992-US9194	19921026
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
US 5234947	A	19930810	US 1991-790387	19911107
AU 9228962	A1	19930607	AU 1992-28962	19921026
EP 663824	A1	19950726	EP 1992-922828	19921026
PRAI US 1991-790387		19911107		
WO 1992-US9194		19921026		

OS MARPAT 119:86044
GI

/ Structure 2 in file .gra /

AB A method for activating K channels and for treating any condition which is treatable by K channel activators, such as hypertension, comprises administering a compd. (I, X is a satd. or unsatd. group having 1-4 C which is optionally substituted by lower alkyl, lower alkenyl or lower alkoxy groups; R1 is H, lower alkyl, lower alkenyl, or aralkyl). Avena pyrone, extd. from Avena sativa, activated the large K channel of membranes from rat ***brain*** .

L8 ANSWER 21 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
AN 1991:30302 BIOSIS
DN BA91:19653
TI HEMODYNAMIC PROFILE OF THE ***POTASSIUM*** ***CHANNEL*** ***ACTIVATOR*** EMD-52692 IN ANESTHETIZED PIGS.
AU SASSEN L M A; DUNCKER D J G M; GHO B C G; DIEKMANN H W; VERDOUW P D
CS LAB. FOR EXPERIMENTAL CARDIOL., THOARAXCENT., ERASMUS UNIV. ROTTERDAM,
P.O. BOX 1738, 3000 DR ROTTERDAM.
SO BR J PHARMACOL, (1990) 101 (3), 605-614.
CODEN: BJPCBM. ISSN: 0007-1188.
FS BA; OLD
LA English
AB 1 The systemic and regional haemodynamic effects of the ***potassium*** ***channel*** ***activator*** EMD 52692 or its solvent were investigated after intravenous and after intracoronary administration in anaesthetized pigs. 2 Consecutive intravenous 10 min infusions of EMD 52692 (0.15, 0.30, 0.60, 1.20 .mu.g kg-1 min-1; n = 7) dose-dependently decreased mean arterial blood pressure by up to 50%. This was entirely due to peripheral vasodilatation, since cardiac output did not change. Heart rate increased by up to 50%, while left ventricular end diastolic pressure decreased dose-dependently from 6 .+-. 1 mmHg to 3 .+-. 1 mmHg (P < 0.05), and stroke volume decreased from 30 .+-. 2 ml to 21 .+-. 2 ml (P < 0.05). Left ventricular dP/dtmax was not affected. 3 Although cardiac output did not change, EMD 52692 caused a redistribution of blood flow from the arteriovenous anastomoses to the capillary channels. Blood flow to the adrenals, small intestine, stomach, bladder, spleen and ***brain*** increased, while renal blood flow decreased and blood flow to several muscle groups and skin were not altered. Vascular conductance was increased dose-dependently in all organs, except for the kidneys, where after the initial increase, vascular conductance returned to baseline with the highest dose. Particularly striking were the effects on the vasculature of the ***brain*** . With the highest dose of EMD 52692 blood flow more than doubled, while vascular conductance increased four fold. 4 Transmural myocardial blood flow increased slightly, which was entirely due to an increase in subepicardial blood flow. Myocardial O2-consumption and segment length shortening were not significantly affected. 5 After consecutive 10 min intracoronary infusions (0.0095, 0.019, 0.0375 and 0.075 .mu.g kg-1 min-1; n = 7) into the left anterior descending coronary artery (LADCA), mean arterial blood pressure was maintained with the lowest two doses, but decreased by up to 15% with the higher doses, whereas heart rate increased by up to 24%. Blood flow to the LADCA-perfused myocardium doubled with the highest dose, the subepicardium benefitting the most. Coronary venous O2-saturation increased dose-dependently from 23 .+-. 2% to 60 .+-. 4%, while myocardial O2-consumption of the LADCA-perfused myocardium was not affected by the drug. 6 It is concluded that EMD 52692 is a potent vasodilator, with particularly pronounced effects on vasculature of the ***brain*** . Its selectivity for vascular smooth muscle cells exceeds that for the myocytes, since with doses that are much higher than those of potential clinical interest no negative inotropic effects were observed. The compound primarily dilates arteries but some venodilatation may also occur.

L8 ANSWER 22 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1990:565291 CAPLUS
DN 113:165291
TI Potassium channel activators abolish excitotoxicity in cultured hippocampal pyramidal neurons
AU Abele, April E.; Miller, Richard J.
CS Dep. Pharmacol. Physiol. Sci., Univ. Chicago, Chicago, IL, 60637, USA
SO Neurosci. Lett. (1990), 115(2-3), 195-200
CODEN: NELED5; ISSN: 0304-3940
DT Journal
LA English
AB When hippocampal pyramidal neurons are grown in culture they develop excitatory synaptic contacts. If these cultures are perfused with Mg2+-free, glycine supplemented medium the neurons exhibit fluctuations in [Ca2+]i and assocd. cell death (excitotoxicity). These phenomena involve the activation of NMDA receptors. When cultures are treated with the K+-channel activators cromakalim and diazoxide both the [Ca2+]i fluctuations and the neuronal death are abolished. These effects are reversed by the sulfonylurea glyburide. It thus appears that K+-channel activators may be a novel therapeutic intervention in epilepsy and assocd. disorders.

L8 ANSWER 23 OF 26 CAPLUS COPYRIGHT 2001 ACS
AN 1990:422 CAPLUS
DN 112:422
TI Effects of cromakalim (BRL 34915) on potassium conductances in CA3 neurons
of the guinea pig hippocampus in vitro
AU Alzheimer, C.; Sutor, B.; Ten Bruggencate, G.
CS Physiol. Inst., Univ. Munich, Munich, D-8000/2, Fed. Rep. Ger.
SO Naunyn-Schmiedeberg's Arch. Pharmacol. (1989), 340(4), 465-71
CODEN: NSAPCC; ISSN: 0028-1298
DT Journal
LA English
AB The action of the ***potassium*** ***channel*** ***activator*** , cromakalim (BRL 34915), on membrane potential, input resistance and current-voltage-relationship of CA3 neurons in a slice prepn. of the guinea-pig hippocampus was investigated by means of intracellular recordings. In the presence of tetrodotoxin, cromakalim (30-100 .mu.mol/L) produced a hyperpolarization up to 4 mV assocd. with a decrease in input resistance up to 10 MOhms. Detn. of the equil. potential of the cromakalim action revealed that the hyperpolarization is due to the activation of a potassium conductance. This cromakalim-activated potassium conductance was voltage-dependent, i.e., it increased with hyperpolarization. Among a no. of potassium channel blockers tested, only Cs+ (2 mmol/L) and Ba2+ (0.5 mmol/L) were able to inhibit the cromakalim-induced effects. Simultaneously, both cations suppressed the hyperpolarizing inward rectification (anomalous rectification) in these neurons, indicating that cromakalim activated or potentiated an inwardly rectifying potassium conductance. In addn., cromakalim slightly enhanced both amplitude and duration of afterhyperpolarizations following single calcium-dependent action potentials, suggesting that cromakalim might have

a weak facilitatory effect on calcium-dependent potassium conductances.

L8 ANSWER 24 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1988:268243 BIOSIS
DN BA86:7487
TI MECHANISM OF ACTION AND SYSTEMIC AND REGIONAL HEMODYNAMICS OF THE
POTASSIUM ***CHANNEL*** ***ACTIVATOR*** BRL-34915 AND ITS
ENANTIOMERS.
AU HOF R P; QUAST U; COOK N S; BLARER S
CS CARDIOVASC. UNIT PRECLIN. RES., SANDOZ LTD., CH-4002 BASEL, SWITZ.
SO CIRC RES, (1988) 62 (4), 679-686.
CODEN: CIRUAL. ISSN: 0009-7330.
FS BA; OLD
LA English
AB BRL34915 (BRL) is a vasodilator with a novel structure. Its mechanism of action, its effects on depolarization-induced and receptor-mediated blood vessel contraction, and its hemodynamic effects were investigated. In the rat portal vein, BRL inhibited spontaneous mechanical activity [IC50 0.013 .+-. 0.001 .mu.M (mean .+-. SEM) for (-)-BRL], the initial effect being a reduced frequency of contraction. At higher concentrations, the spontaneous contractions were abolished and 86Rb+ efflux was increased. These results suggest that BRL preferentially acts on the pacemaker cells, the K+ channels in other cells being activated only at higher BRL concentrations in this vessel. In experiments on the rabbit aorta, (-)-BRL shifted the KCl concentration-response curve to the right and noncompetitively inhibited responses to angiotensin II. A concentration of 3 .mu.M (-)-BRL reduced maximal angiotensin II contractions by around 50%, higher concentrations having little further effect. This inhibition of angiotensin II contractions is notably greater than that seen with Ca2+ antagonists in this vessel. In anesthetized rabbits, (-)-BRL was a peripheral vasodilator at doses of 3-30 .mu.g/kg, but it had no relevant effects on heart rate and myocardial contractile force. This suggests tissue selectivity of this compound or this mechanism of action. BRL preferentially dilated the coronary, gastrointestinal, and cerebral vessels but not those of the kidneys or skeletal muscle as measured with tracer microspheres. This profile of activity is different from that of calcium antagonists or nonspecific vasodilators like dihydralazine. All effects were stereoselective, the (-)-enantiomer being 100 to 200 times more active than the (+)-enantiomer.

L8 ANSWER 25 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
AN 88176946 EMBASE
DN 1988176946
TI The ***potassium*** ***channel*** ***activator*** , BRL 34915, antagonises a behavioural response to the muscarinic receptor agonist, pilocarpine.
AU Tricklebank M.D.; Flockhart G.; Freedman S.B.
CS Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre,
Harlow CM20 2QR, United Kingdom
SO European Journal of Pharmacology, (1988) 151/2 (349-350).
ISSN: 0014-2999 CODEN: EJPHAZ
CY Netherlands
DT Journal
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Muscarinic acetylcholine receptor agonists induce an influx of calcium into neurons resulting in an activation of calcium-dependent potassium channels and slow neuronal depolarisation. This implies that the pharmacological opening of potassium channels can reduce the neuronal response to acetylcholine receptor agonists. Consistent with this hypothesis, we now show that the direct injection of the ***potassium*** ***channel*** ***activator*** , BRL 34915 ((+)-6-cyano-3,4-dihydro-2,2-dimethyl-trans-(2-oxo-1-pyrrolidyl)-2H-b nzo[b]-pyran-3-ol), into the mouse ***brain*** can inhibit a behavioural response to the muscarinic receptor agonist, pilocarpine.

L8 ANSWER 26 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 5
AN 1988:53397 BIOSIS
DN BA85:30256
TI SPECIFICITY OF ACTION OF THE NOVEL ANTIHYPERTENSIVE AGENT BRL-34915 AS A
POTASSIUM ***CHANNEL*** ***ACTIVATOR*** COMPARISON WITH
NICORANDIL.
AU COLDWELL M C; HOWLETT D R
CS BEECHAM PHARM., MED. RES. CENT., COLDHARBOUR ROAD, THE PINNACLES, HARLOW,
ESSEX, U.K.
SO BIOCHEM PHARMACOL, (1987) 36 (21), 3663-3670.
CODEN: BCPCA6. ISSN: 0006-2952.
FS BA; OLD
LA English
AB Experiments have been performed to investigate the specificity of the mechanism of action of the novel antihypertensive agent, BRL 34915. BRL 34915 (0.5-100 .mu.) and nicorandil (10-500 .mu.M) stimulated the efflux of rubidium from preloaded rabbit isolated mesenteric arteries. BRL 34915 also caused an increase in the rubidium efflux rate constant in other vascular smooth muscles. Tetraethylammonium (0.1-30 mM) inhibited BRL 34915 (10 .mu.M), nicorandil (100 .mu.M) and potassium (30 mM) induced stimulations of rubidium efflux, but had no effect on noradrenaline (30 .mu.M) induced efflux. Only noradrenaline induced efflux was inhibited by apamin (3-100 nM). Examination of other second messenger systems demonstrated that BRL 34915 (at concentrations up to 100 .mu.M) did not have any appreciable effect on cGMP accumulation in rabbit mesenteric artery, cAMP or cGMP phosphodiesterase in rat heart, or cAMP and inositol phosphate accumulation in rat ***brain*** slices. Nicorandil (100 .mu.M) caused a small increase in cGMP accumulation in rabbit mesentric artery. Radioligand binding studies showed that BRL 34915 did not interact with dihydropyridine, 5-hydroxytryptamine, dopamine, .alpha.1, .alpha.2 or .beta. adrenoceptor binding sites. [3H]-BRL 34915 did not bind specifically to any site in any tissue studied, either in vitro or ex vivo. Thus we have been unable to demonstrate an effect of BRL 34915 other than of increasing potassium efflux in rabbit vascular smooth muscle. This lends support to other evidence suggesting that BRL 34915 relaxes vascular smooth muscle (and hence lowers blood pressure) by a novel, and specific, mechanism involving hyperpolarisation of the smooth muscle cell membrane.

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LAST RELOADED: Nov 9, 2001 (20011109/UP).

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=> s potassium channel activator? or potassium channel openner?
0 POTASSIUM
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L9 0 POTASSIUM CHANNEL ACTIVATOR? OR POTASSIUM CHANNEL OPENNER?

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FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 10:58:25 ON 14 NOV 2001
L1 566 S POTASSIUM CHANNEL ACTIVATOR
L2 29 S PERMEABILITY AND BRAIN AND DELIVER
L3 0 S L1 AND L2
L4 0 S L1 AND PERMEABLILITY
L5 6 S L1 AND PERMEABILITY
L6 6 DUP REM L5 (0 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 11:07:08 ON 14 NOV 2001

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:10:47 ON 14 NOV 2001

FILE 'STNGUIDE' ENTERED AT 11:10:54 ON 14 NOV 2001

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:15:06 ON 14 NOV 2001
L7 35 S L1 AND BRAIN
L8 26 DUP REM L7 (9 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 11:22:05 ON 14 NOV 2001
L9 0 S POTASSIUM CHANNEL ACTIVATOR? OR POTASSIUM CHANNEL OPENNER?

FILE 'BIOSIS' ENTERED AT 11:43:27 ON 14 NOV 2001

=> s potassium channel activator? or potassium channel openner?
187387 POTASSIUM
110540 CHANNEL
65767 ACTIVATOR?
305 POTASSIUM CHANNEL ACTIVATOR?
(POTASSIUM(W)CHANNEL(W)ACTIVATOR?)
187387 POTASSIUM
110540 CHANNEL
0 OPENNER?
0 POTASSIUM CHANNEL OPENNER?
(POTASSIUM(W)CHANNEL(W)OPENNER?)
L10 305 POTASSIUM CHANNEL ACTIVATOR? OR POTASSIUM CHANNEL OPENNER?

=> s l10 and brain
379365 BRAIN
L11 7 L10 AND BRAIN

=> d bib abs

L11 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:509497 BIOSIS
DN PREV200100509497
TI Diazoxide, but not cyclosporin A or hypothermia, preserves N-methyl-D-aspartate (NMDA)-induced cerebral dilation after ischemia in piglets.
AU Busija, D. W. (1); Perciaccante, J. (1); Domoki, F. (1)
CS (1) Physiology/Pharmacology, Wake Forest Univ. School of Medicine, Winston-Salem, NC USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 887. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DT Conference
LA English
SL English
AB We have previously shown that diazoxide, a specific activator of mitochondrial ATP-sensitive potassium channels (mKATP), preserves vascular dilator responses to application of NMDA after ischemia (Stroke 30:2713-2718, 1999). We also have shown that diazoxide administration limits infarct volume in neonatal and adult rats following cerebral ischemia. In addition, other interventions that affect mitochrondial function, such as cyclosporin A (CsA) administration and ***brain*** cooling, also reduce infarct size after ischemia. Thus, we assessed whether CsA and hypothermia were as effective as diazoxide in protecting neuronal function against ischemia. We examined effects of NMDA in anesthetized piglets on pial arteriolar diameter before ischemia and 1 hour after 10 min of global ischemia in three groups: diazoxide pretreated (10-5M; n=5), CsA pretreated (10-4M; n=6), and local ***brain*** cooling (34degreeC; n=11). Total ***brain*** ischemia was induced by increasing intracranial pressure. In the diazoxide group, arterioles (baseline diameterapprx100 microns) dilated by 15+-9% versus 14+-5% at 5X10-5M NMDA (ns) and by 41+-13% versus 39+-8% at 10-4M NMDA (ns), before and after ischemia, respectively. In the CsA group, arteriolar dilation was reduced (p<.05) by ischemia to 6+-4% at 5X10-5M NMDA and 13+-8% at 10-4M NMDA. In the hypothermia group, dilation was reduced to 8+-5% at 5X10-5M NMDA and 20+-5% at 10-4M NMDA after ischemia (p<.05). We conclude that diazoxide has specific neuroprotective effects via KATP on neuronal function in the early post-ischemic period.

=> d bib abs 2-
YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y

L11 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:71517 BIOSIS
DN PREV200100071517
TI Inhibition of imidazoline I2 site binding by potassium channel modulators.
AU Slattery, D. A. (1); Hudson, A. L. (1); Nutt, D. J. (1)
CS (1) Psychopharmacology Unit, University of Bristol, Bristol, BS8 1TD UK
SO British Journal of Pharmacology, (October, 2000) Vol. 131, No. Proceedings Supplement, pp. 39P. print.
Meeting Info.: Meeting of the British Pharmacological Society Cardiff, Wales, UK July 12-14, 2000 British Pharmacological Society
. ISSN: 0007-1188.
DT Conference
LA English
SL English

L11 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:77799 BIOSIS
DN PREV199799384502
TI The effect of the ***potassium*** ***channel*** ***activator*** , cromakalim, on antidepressant drugs in the forced swimming test in mice.
AU Redrobe, J. P.; Pinot, P.; Bourin, M. (1)
CS (1) Dep. Pharmacol., GIS Medicament, 1 rue Gaston Veil, 44035 Nantes cedex
France
SO Fundamental & Clinical Pharmacology, (1996) Vol. 10, No. 6, pp. 524-528.
ISSN: 0767-3981.
DT Article
LA English
AB The forced swimming test (FST) is a widely used behavioural model to predict potential antidepressant (AD) action of compounds in humans. It has been previously shown that pretreatment with lithium, quinine and clonidine had additive effects on AD drugs in the FST, an effect proposed to be a result of potassium channel blockade. It is possible that pretreatment with potassium channel openers may induce opposite effects to those seen following pretreatment with potassium channel blockers in the FST. Pretreatment with cromakalim (CROM) (1 mg/kg, intraperitoneally (ip)) antagonized the anti-immobility effects of the mixed noradrenaline (NA)/5-hydroxytryptamine (5-HT)reuptake inhibitors imipramine and amitriptyline (P lt 0.05). CROM administration (0.06 and 1 mg/kg, ip) also blocked the AD-like effects of the specific NA reuptake inhibitor, desipramine, and the selective serotonin reuptake inhibitor, paroxetine (P lt 0.05 and P lt 0.01, respectively). Pretreatment with CROM via gavage (1 mg/kg) antagonized the AD-like effects of imipramine, amitriptyline, desipramine and paroxetine. CROM treatment (via ip route or gavage) did not have any significant effect on the anti-immobility activity of the atypical AD mianserin at any of the doses employed. Another potassium-channel opener, minoxidil (MINOX), which does not cross the blood- ***brain*** barrier, was also tested to eliminate the possibility that CROM may be acting via peripheral/local mechanisms. MINOX (32 mg/kg) failed to antagonize anti-immobility effects of any of the AD tested. In conclusion, the results of the present study suggest that CROM is only acting on drugs involved with neurotransmitter uptake inhibition.

L11 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:466397 BIOSIS
DN PREV199699188753
TI Electrophysiological investigation of adenosine trisphosphate-sensitive potassium channels in the rat substantia nigra pars reticulata.
AU Stanford, I. M.; Lacey, M. G. (1)
CS (1) Dep. Pharmacology, Med. Sch., Univ. Birmingham, Edgbaston, Birmingham
B15 2TT UK
SO Neuroscience, (1996) Vol. 74, No. 2, pp. 499-509.
ISSN: 0306-4522.
DT Article
LA English
AB Adenosine trisphosphate-sensitive potassium (K-ATP) channels in the substantia nigra pars reticulata were studied in rat ***brain*** slices using whole-cell patch clamp recording. Substantia nigra pars reticulata neurons were identified as such by their spontaneous action potential firing at mean rate of 15.3 Hz, virtual absence of hyperpolarization-activated inward current I-h, and unresponsiveness to dopamine (30 mu-M), quinpirole (10 mu-M) and (Met)enkephalin (10 mu-M). Intracellular dialysis with Mg-2+-ATP-free pipette solutions caused a slowly developing membrane hyperpolarization (13 +- 4 mV), accompanied by a cessation of action potential firing, or an outward current (79 +- 30 pA at around -60 mV), which were reversed by the sulphonylurea K-ATP channel blockers tolbutamide (100 mu-M) and glibenclamide (3 mu-M). When Mg-2+-ATP (2 mM) was included in the recording pipette no membrane hyperpolarization or outward current was observed. Neither the sulphonylureas nor the ***potassium*** ***channel*** ***activator*** lemakalim (200 mu-M) altered membrane potential, firing rate or holding current under these recording conditions. The outward current induced by dialysis with Mg-2+-ATP-free solutions reversed polarity negative to -94 +- 9 mV (9 cells), close to the estimated K+ equilibrium potential (-105 mV) for the conditions used, and was associated with a conductance increase that was blocked by Ba-2+ (100 mu-M). The current blocked by the sulphonylureas had a similar reversal potential (-97 +- 7 mV; 13 cells), and both currents were voltage independent over the range -50 to -100 mV with slope conductance of approximately 2.0 nS. Outward synaptic currents were evoked by single shock electrical stimulation, in the presence of glutamate receptor antagonists, at a holding potential of -50 mV. These synaptic currents were blocked by bicuculline (10 mu-M) and reversed polarity at around - 65 mV, close to the Cl- equilibrium potential, and were thus mediated by GABA-A receptors. They were reversibly depressed by 37 +- 14% in lemakalim (200 mu-M) in 6/12 cells tested, an effect that was partially reversed by tolbutamide (200 mu-M). It is concluded that functional K-ATP channels are present both presynaptically and postsynaptically in the substantia nigra pars reticulata. Postsynaptic K-ATP channels may control excitability in conditions where intracellular ATP is reduced, whereas presynaptic K-ATP channels, sensitive to the ***potassium*** ***channel*** ***activator*** lemakalim, can modulate the release of GABA, which probably arises from fibres of extranigral origin. Pharmacological differences between these two sites could be exploited to

treat epilepsies, dyskinesias and akinesia.

L11 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1991:30302 BIOSIS
DN BA91:19653
TI HEMODYNAMIC PROFILE OF THE ***POTASSIUM*** ***CHANNEL*** ***ACTIVATOR*** EMD-52692 IN ANESTHETIZED PIGS.
AU SASSEN L M A; DUNCKER D J G M; GHO B C G; DIEKMANN H W; VERDOUW P D
CS LAB. FOR EXPERIMENTAL CARDIOL., THOARAXCENT., ERASMUS UNIV. ROTTERDAM,
P.O. BOX 1738, 3000 DR ROTTERDAM.
SO BR J PHARMACOL, (1990) 101 (3), 605-614.
CODEN: BJPCBM. ISSN: 0007-1188.
FS BA; OLD
LA English
AB 1 The systemic and regional haemodynamic effects of the ***potassium*** ***channel*** ***activator*** EMD 52692 or its solvent were investigated after intravenous and after intracoronary administration in anaesthetized pigs. 2 Consecutive intravenous 10 min infusions of EMD 52692 (0.15, 0.30, 0.60, 1.20 .mu.g kg-1 min-1; n = 7) dose-dependently decreased mean arterial blood pressure by up to 50%. This was entirely due to peripheral vasodilatation, since cardiac output did not change. Heart rate increased by up to 50%, while left ventricular end diastolic pressure decreased dose-dependently from 6 .+-. 1 mmHg to 3 .+-. 1 mmHg (P < 0.05), and stroke volume decreased from 30 .+-. 2 ml to 21 .+-. 2 ml (P < 0.05). Left ventricular dP/dtmax was not affected. 3 Although cardiac output did not change, EMD 52692 caused a redistribution of blood flow from the arteriovenous anastomoses to the capillary channels. Blood flow to the adrenals, small intestine, stomach, bladder, spleen and ***brain*** increased, while renal blood flow decreased and blood flow to several muscle groups and skin were not altered. Vascular conductance was increased dose-dependently in all organs, except for the kidneys, where after the initial increase, vascular conductance returned to baseline with the highest dose. Particularly striking were the effects on the vasculature of the ***brain*** . With the highest dose of EMD 52692 blood flow more than doubled, while vascular conductance increased four fold. 4 Transmural myocardial blood flow increased slightly, which was entirely due to an increase in subepicardial blood flow. Myocardial O2-consumption and segment length shortening were not significantly affected. 5 After consecutive 10 min intracoronary infusions (0.0095, 0.019, 0.0375 and 0.075 .mu.g kg-1 min-1; n = 7) into the left anterior descending coronary artery (LADCA), mean arterial blood pressure was maintained with the lowest two doses, but decreased by up to 15% with the higher doses, whereas heart rate increased by up to 24%. Blood flow to the LADCA-perfused myocardium doubled with the highest dose, the subepicardium benefitting the most. Coronary venous O2-saturation increased dose-dependently from 23 .+-. 2% to 60 .+-. 4%, while myocardial O2-consumption of the LADCA-perfused myocardium was not affected by the drug. 6 It is concluded that EMD 52692 is a potent vasodilator, with particularly pronounced effects on vasculature of the ***brain*** . Its selectivity for vascular smooth muscle cells exceeds that for the myocytes, since with doses that are much higher than those of potential clinical interest no negative inotropic effects were observed. The compound primarily dilates arteries but some venodilatation may also occur.

L11 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1988:268243 BIOSIS
DN BA86:7487
TI MECHANISM OF ACTION AND SYSTEMIC AND REGIONAL HEMODYNAMICS OF THE ***POTASSIUM*** ***CHANNEL*** ***ACTIVATOR*** BRL-34915 AND ITS ENANTIOMERS.
AU HOF R P; QUAST U; COOK N S; BLARER S
CS CARDIOVASC. UNIT PRECLIN. RES., SANDOZ LTD., CH-4002 BASEL, SWITZ.
SO CIRC RES, (1988) 62 (4), 679-686.
CODEN: CIRUAL. ISSN: 0009-7330.
FS BA; OLD
LA English
AB BRL34915 (BRL) is a vasodilator with a novel structure. Its mechanism of action, its effects on depolarization-induced and receptor-mediated blood vessel contraction, and its hemodynamic effects were investigated. In the rat portal vein, BRL inhibited spontaneous mechanical activity [IC50 0.013 .+-. 0.001 .mu.M (mean .+-. SEM) for (-)-BRL], the initial effect being a reduced frequency of contraction. At higher concentrations, the spontaneous contractions were abolished and 86Rb+ efflux was increased. These results suggest that BRL preferentially acts on the pacemaker cells, the K+ channels in other cells being activated only at higher BRL concentrations in this vessel. In experiments on the rabbit aorta, (-)-BRL shifted the KCl concentration-response curve to the right and noncompetitively inhibited responses to angiotensin II. A concentration of 3 .mu.M (-)-BRL reduced maximal angiotensin II contractions by around 50%, higher concentrations having little further effect. This inhibition of angiotensin II contractions is notably greater than that seen with Ca2+ antagonists in this vessel. In anesthetized rabbits, (-)-BRL was a peripheral vasodilator at doses of 3-30 .mu.g/kg, but it had no relevant effects on heart rate and myocardial contractile force. This suggests tissue selectivity of this compound or this mechanism of action. BRL preferentially dilated the coronary, gastrointestinal, and cerebral vessels but not those of the kidneys or skeletal muscle as measured with tracer microspheres. This profile of activity is different from that of calcium antagonists or nonspecific vasodilators like dihydralazine. All effects were stereoselective, the (-)-enantiomer being 100 to 200 times more active than the (+)-enantiomer.

L11 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1988:53397 BIOSIS
DN BA85:30256
TI SPECIFICITY OF ACTION OF THE NOVEL ANTIHYPERTENSIVE AGENT BRL-34915 AS A ***POTASSIUM*** ***CHANNEL*** ***ACTIVATOR*** COMPARISON WITH NICORANDIL.
AU COLDWELL M C; HOWLETT D R
CS BEECHAM PHARM., MED. RES. CENT., COLDHARBOUR ROAD, THE PINNACLES, HARLOW, ESSEX, U.K.
SO BIOCHEM PHARMACOL, (1987) 36 (21), 3663-3670.
CODEN: BCPCA6. ISSN: 0006-2952.
FS BA; OLD
LA English
AB Experiments have been performed to investigate the specificity of the mechanism of action of the novel antihypertensive agent, BRL 34915. BRL 34915 (0.5-100 .mu.) and nicorandil (10-500 .mu.M) stimulated the efflux of rubidium from preloaded rabbit isolated mesenteric arteries. BRL 34915 also caused an increase in the rubidium efflux rate constant in other vascular smooth muscles. Tetraethylammonium (0.1-30 mM) inhibited BRL 34915 (10 .mu.M), nicorandil (100 .mu.M) and potassium (30 mM) induced stimulations of rubidium efflux, but had no effect on noradrenaline (30 .mu.M) induced efflux. Only noradrenaline induced efflux was inhibited by apamin (3-100 nM). Examination of other second messenger systems demonstrated that BRL 34915 (at concentrations up to 100 .mu.M) did not have any appreciable effect on cGMP accumulation in rabbit mesenteric artery, cAMP or cGMP phosphodiesterase in rat heart, or cAMP and inositol phosphate accumulation in rat ***brain*** slices. Nicorandil (100 .mu.M) caused a small increase in cGMP accumulation in rabbit mesentric artery. Radioligand binding studies showed that BRL 34915 did not interact with dihydropyridine, 5-hydroxytryptamine, dopamine, .alpha.1, .alpha.2 or .beta. adrenoceptor binding sites. [3H]-BRL 34915 did not bind specifically to any site in any tissue studied, either in vitro or ex vivo. Thus we have been unable to demonstrate an effect of BRL 34915 other than of increasing potassium efflux in rabbit vascular smooth muscle. This lends support to other evidence suggesting that BRL 34915 relaxes vascular smooth muscle (and hence lowers blood pressure) by a novel, and specific, mechanism involving hyperpolarisation of the smooth muscle cell membrane.

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NEWS 4 Feb 01 DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5 Feb 19 Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6 Mar 08 Gene Names now available in BIOSIS

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NEWS 8 Mar 22 TRCTHERMO no longer available
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=> s (activat? or stimulat?) (3a) soluble guanylyl cyclase
L1 749 (ACTIVAT? OR STIMULAT?) (3A) SOLUBLE GUANYLYL CYCLASE

=> s l1 and (blood brain barrier or blood tumor barrier)
L2 0 L1 AND (BLOOD BRAIN BARRIER OR BLOOD TUMOR BARRIER)

=> s l1 and permeab?
L3 37 L1 AND PERMEAB?

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L4 ANSWER 1 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2002:173363 BIOSIS
DN PREV200200173363
TI Possible involvement of nitric oxide in signaling pigment dispersion in teleostean melanophores.
AU Hayashi, Hiroshi; Fujii, Ryozo (1)
CS (1) 3-22-15 Nakaizumi, Tokyo, 201-0012: ryo-fujii@par.odn.ne.jp Japan
SO Zoological Science (Tokyo), (December, 2001) Vol. 18, No. 9, pp. 1207-1215. print.
ISSN: 0289-0003.
DT Article
LA English
AB The possible involvement of nitric oxide (NO) in regulating the motile activities of teleostean melanophores was studied in the dark chub Zacco temmincki (Cyprinidae, Cypriniformes) and in the translucent glass catfish Kryptopterus bicirrhis (Siluridae, Siluriformes). NO donors, including (+-)-(E)-methyl-2-((E)-hydroxyimino)-5-nitro-6-methoxy-3-hexaneamide (NOR 1), molsidomine (MSD), sodium nitroprusside (SNP) and glyceryl trinitrate (GTN), had no pigment-aggregating action on melanophores, but actively dispersed melanosomes in those cells. Among those reagents, NOR 1, a spontaneous releaser of NO, was the most effective. Inhibitors for nitric oxide synthase (NOS), i.e. Nomega-nitro-L-arginine methyl ester (L-NNA), Nomega-nitro-L-arginine (L-NAME) and Nomega-monomethyl-L-arginine (L-NMMA), showed melanosome-aggregating effects. A membrane-***permeable*** analogue of cyclic guanosine-3',5'-monophosphate (8-Br-cGMP) was effective in dispersing melanosomes. The sum of these results suggests that NO plays an active role in the elaborate control of color changes in teleosts by dispersing pigment in melanophores via ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** to increase cytosolic levels of cGMP.

L4 ANSWER 2 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2001:566784 BIOSIS
DN PREV200100566784
TI Prolonged exposure to YC-1 induces apoptosis in adrenomedullary endothelial and chromaffin cells through a cGMP-independent mechanism.
AU Ferrero, R.; Torres, M. (1)
CS (1) Departamento de Bioquimica, Facultad de Veterinaria, Universidad Complutense de Madrid, 28040, Madrid: mitorres@eucmax.sim.ucm.es Spain
SO Neuropharmacology, (December, 2001) Vol. 41, No. 7, pp. 895-906. print.
ISSN: 0028-3908.
DT Article
LA English
SL English
AB YC-1, a benzyl indazole derivative, is an NO-independent direct ***activator*** of ***soluble*** ***guanylyl*** ***cyclase*** (sGC), which presents a synergistic action with NO in stimulating cGMP synthesis. These properties have served to suggest YC-1 as an attractive therapeutic agent by permitting the reduction of nitrovasodilator dosage and regulating endogenous cGMP metabolism. Here we studied the effect of prolonged exposure of adrenomedullary endothelial and chromaffin cells to YC-1. We found that YC-1 increased cGMP in the two types of cells and this action was blocked by the sGC inhibitor 1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one (ODQ). Cells underwent apoptotic death in association with increased caspase-3-like activity, DNA fragmentation, cytoskeletal disorganization and changes in membrane ***permeability*** after prolonged incubation with YC-1. Caspase-3-like protease activity and DNA fragments in the cytoplasm were increased in a dose-dependent manner by 16 h YC-1 treatment. The specific and cell ***permeable*** caspase-3-like protease inhibitor DEVD-CHO effectively inhibited YC-1-mediated caspase-3-like activation and DNA fragmentation. Moreover, YC-1 also induced cell shape changes accompanied by actin filament disorganization and alterations in membrane ***permeability*** . Cells incubated for 24 h with YC-1 showed damaged membranes by binding to nucleic acid of a dye excluded by the intact plasma membrane of live cells. YC-1 also induced a decrease in the intracellular non-specific esterase activity, another indication of cell toxicity. Apoptotic phenomena were not prevented by the presence of ODQ although it effectively inhibited the YC-1-elicited cGMP increases. These findings indicate that YC-1 induces apoptosis by activating caspase-3-like protease through a mechanism independent of sGC activation.

L4 ANSWER 3 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001087730 EMBASE
TI Sources and targets of nitric oxide signalling in insect nervous systems.
AU Bicker G.
CS G. Bicker, Inst. Tierokologie und Zellbiologie, Tierarztliche Hochschule Hannover, Bunteweg 17d, 30559 Hannover, Germany. gbicker@zellbiologie.tiho-hannover.de
SO Cell and Tissue Research, (2001) 303/2 (137-146).
Refs: 100
ISSN: 0302-766X CODEN: CTSRCS
CY Germany
DT Journal; General Review
FS 004 Microbiology
LA English
SL English
AB Nitric oxide (NO) is a membrane permeant signalling molecule which ***activates*** ***soluble*** ***guanylyl*** ***cyclase*** and leads to the formation of cyclic GMP (cGMP) in target cells. In the nervous system, NO/cGMP signalling is thought to play essential roles in synaptic plasticity during development and also in the mature animal. This review summarizes neurochemical, cell biological, and physiological investigations of NO/cGMP signalling in the nervous system of insects. The anatomical localization of donor and target cells suggests functions in olfaction, vision, and mechanosensation. Behavioural assays have uncovered contributions of NO signalling in oxygen sensing, habituation to chemosensory stimuli, and associative memory formation. During development, NO regulates cell proliferation, axonal outgrowth, and synaptic maturation. The cellular distribution of NO-responsive cells suggests that NO can serve as a retrograde synaptic messenger, as an intracellular messenger, and as a lateral diffusible messenger irrespective of conventional synaptic connectivity.

L4 ANSWER 4 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:222127 BIOSIS
DN PREV200200222127
TI Increased cGMP levels mediate oxidant-induced disruption of microtubule (MT) cytoskeleton and increased ***permeability*** of monolayers of

human intestinal cells.
AU Komanduri, Sri (1); Banan, Ali (1); Zhang, Yang (1); Keshavarzian, Ali (1)
CS (1) Rush Univ, Chicago, IL USA
SO Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.694. http://www.gastrojournal.org/. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week Atlanta, Georgia, USA May 20-23, 2001
ISSN: 0016-5085.
DT Conference
LA English

L4 ANSWER 5 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 1999:403502 BIOSIS
DN PREV199900403502
TI Ovarian hormone dependence of alpha1-adrenoceptor activation of the nitric oxide-cGMP pathway: Relevance for hormonal facilitation of lordosis behavior.
AU Chu, Hsiao-Pai; Etgen, Anne M. (1)
CS (1) Department of Neuroscience, F113, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY, 10461 USA
SO Journal of Neuroscience, (Aug. 15, 1999) Vol. 19, No. 16, pp. 7191-7197.
ISSN: 0270-6474.
DT Article
LA English
SL English
AB The ovarian hormones estradiol (E2) and progesterone (P) facilitate rat lordosis behavior in part by regulating the expression of and signal transduction by adrenoceptors in the hypothalamus (HYP) and preoptic area (POA). The major adrenoceptor subtype mediating E2 and P facilitation of lordosis is the alpha1-adrenoceptor. In the present studies, we tested the hypotheses that (1) alpha1-adrenoceptors in the HYP enhance lordosis responses by activating the nitric oxide (NO)-cGMP signaling pathway, and (2) coupling of alpha1-adrenoceptors to this signal transduction pathway is hormone-dependent. Basal levels of cGMP were significantly higher in HYP and POA slices from animals treated with E2 and P when compared with slices from ovariectomized controls or females treated with only E2 or P. When slices of HYP and POA from ovariectomized female rats were incubated with norepinephrine or the selective alpha1-adrenoceptor agonist phenylephrine, cGMP accumulation was observed only if slices had been derived from females treated with both E2 and P before experimentation. Moreover, alpha1-adrenoceptor stimulation of cGMP synthesis was blocked by an inhibitor of NO synthase, confirming that these receptors act by NO-mediated ***stimulation*** of ***soluble*** ***guanylyl*** ***cyclase*** . Behavioral studies demonstrated further that the cell-***permeable*** cGMP analog 8-bromoadenosine-cGMP reverses the inhibitory effects of the alpha1-adrenoceptor antagonist prazosin on lordosis behavior in E2- and P-treated female rats. Thus, the NO-cGMP pathway mediates the facilitatory effects of alpha1-adrenoceptors on lordosis behavior in female rats, and previous exposure of the HYP and POA to both E2 and P are required to link alpha1-adrenoceptors to this pathway.

L4 ANSWER 6 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999182646 EMBASE
TI Nitric oxide via cGMP-dependent mechanisms increases dye coupling and excitability of rat supraoptic nucleus neurons.
AU Yang Q.Z.; Hatton G.I.
CS Dr. G.I. Hatton, Department of Neuroscience, University of California, Riverside, CA 92521, United States
SO Journal of Neuroscience, (1 Jun 1999) 19/11 (4270-4279).
Refs: 50
ISSN: 0270-6474 CODEN: JNRSDS
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
LA English
SL English
AB Unlike many neuron populations, supraoptic nucleus (SON) neurons are rich in both nitric oxide synthase (NOS) and the NO receptor- ***soluble*** ***guanylyl*** ***cyclase*** (GC), the ***activation*** of which leads to cGMP accumulation. Elevations in cGMP result in increased coupling among SON neurons. We investigated the effect of NO on dye coupling in SONs from male, proestrus virgin female, and lactating rats. In 167 slices 263 SON neurons were recorded; 210 of these neurons were injected intracellularly (one neuron per SON) with Lucifer yellow (LY). The typically minimal coupling seen in virgin females was increased nearly fourfold by the NO precursor, L-arginine, or the NO donor, sodium nitroprusside (SNP). L-Arginine-induced coupling was abolished by a NOS inhibitor. In slices from male and lactating rats who have a higher basal incidence of coupling, SNP increased coupling by approximately twofold over control ($p < 0.03$). SNP effects were prevented by the NO scavenger hemoglobin (20 .mu.M) and by the selective blocker of NO-activated GC, ODQ (10 .mu.M). These results suggest that NO released from cells within the SON can expand the coupled network of neurons and that this action occurs via cGMP-dependent processes. Because increased coupling is associated with elevated SON neuronal excitability, we also studied the effects of 8-bromo-cGMP on excitability. In both phasically and continuously firing neurons 8-bromo- cGMP (1-2 mM), but not cGMP, produced membrane depolarizations accompanied by membrane conductance increases.
Conductance
increases remained when depolarizations were eliminated by current-clamping the membrane potential. Thus, NO-induced cGMP increases SON neuronal coupling and excitability.

L4 ANSWER 7 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 1999:13001 BIOSIS
DN PREV199900013001
TI The NO-cGMP pathway in the rat locus coeruleus: Electrophysiological, immunohistochemical and in situ hybridization studies.
AU Xu, Zhi-Qing David (1); De Vente, Jan; Steinbusch, Harry; Grillner, Sten; Hokfelt, Tomas
CS (1) Dep. Neurosci., Karolinska Inst., S-17177 Stockholm Sweden
SO European Journal of Neuroscience, (Nov., 1998) Vol. 10, No. 11, pp. 3508-3516.
ISSN: 0953-816X.
DT Article
LA English
AB The effect of two nitric oxide (NO) donors, SIN-1 and DEA/NO, as well as of the inactive SIN-1 derivative molsidomin, was studied on locus coeruleus (LC) neurons in a slice preparation using intracellular recordings. In addition, the effect of the guanylate cyclase inhibitor ODQ was analysed. Furthermore, the effect of NO donors on cyclic guanosine monophosphate (GMP) levels in the LC was studied using the indirect immunofluorescence technique, and the expression of soluble guanylyl cyclase with in situ hybridization. In 36 of 66 LC neurons extracellular application of SIN-1 and DEA/NO caused a hyperpolarization and a decrease in apparent input resistance. In almost 20% of neurons SIN-1 increased the firing rate. No effect could be recorded with the brain-inactive SIN-1 derivative molsidomin. The membrane ***permeable*** cGMP analogue 8-bromo-cGMP imitated the action of SIN-1. The hyperpolarizing effect of SIN-1 and DEA/NO was attenuated by preincubation with the guanylyl cyclase inhibitor ODQ. The immunohistochemical analysis revealed lack of cGMP immunostaining in non-stimulated slices, whereas SIN-1 dramatically increased this staining in about 40% of the LC neurons, and these neurons were all tyrosine hydroxylase positive, that is noradrenergic. A large proportion of the LC neurons expressed soluble guanylyl cyclase mRNA. The present and previous results suggest that NO, released from a small number of non-noradrenergic neurons in the LC, mainly has an inhibitory influence on many noradrenergic neurons, by upregulating cGMP levels via ***stimulation*** of ***soluble*** ***guanylyl*** ***cyclase*** . As nitric oxide synthase is present only in a small number of non-noradrenergic neurons (Xu et al., 1994), a few neurons may influence a large population of noradrenergic LC neurons, which in turn may control activity in many regions of the central nervous system.

L4 ANSWER 8 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998143571 EMBASE
TI Molecular actions of a Mn(III)porphyrin superoxide dismutase mimetic and peroxynitrite scavenger: Reaction with nitric oxide and direct inhibition of NO synthase and soluble guanylyl cyclase.
AU Pfeiffer S.; Schrammel A.; Koesling D.; Schmidt K.; Mayer B.
CS B. Mayer, Inst. fur Pharmakologie/Toxikologie, Karl-Franzens-Universitat Graz, Universitatsplatz 2, A-8010 Graz, Austria. mayer@kfunigraz.ac.at
SO Molecular Pharmacology, (1998) 53/4 (795-800).
Refs: 36
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin (MnTMPyP), described as a superoxide dismutase mimetic and peroxynitrite scavenger, has been used previously to investigate the cytotoxic potential of superoxide and peroxynitrite in several pathological models. Here we report on the interference of MnTMPyP with NO/cGMP signaling using cultured endothelial cells as well as purified ***soluble*** ***guanylyl*** ***cyclase*** (sGC) either ***activated*** by the NO donor 2,2-diethyl-1-nitroso-oxyhydrazine sodium salt (DEA/NO) or reconstituted with nitric oxide synthase (NOS). MnTMPyP inhibited endothelial cGMP accumulation induced by A23187 (0.3 .mu.M) with an IC50 of 75.0 .+-. 10.4 .mu.M but had no significant effect on the potency of the Ca2+ ionophore. Purified NOS was inhibited by MnTMPyP (IC50 = 5.5 .+-. 0.8 .mu.M) because of an interference of the Mn-porphyrin with the reductase domain of the enzyme. The most pronounced actions of MnTMPyP were direct inhibition of sGC and scavenging of NO. Purified sGC stimulated with either Ca2+/calmodulin- activated NOS (in the presence of GSH) or DEA/NO (in the absence of GSH) was inhibited with IC50 values of 0.8 .+-. 0.09 .mu.M and 0.6 .+-. 0.2 .mu.M, respectively. In the presence of GSH, MnTMPyP was reduced to the Mn(II) complex, resulting in efficient scavenging of NO under these conditions. Our data demonstrate that MnTMPyP (i) interferes with the reductase domain of NOS, (ii) scavenges NO in the presence of GSH, and (iii) is a potent direct inhibitor of sGC. These results cast doubt on the usefulness of MnTMPyP and related Mn-porphyrin complexes as probes to study the involvement of peroxynitrate/superoxide in biological systems.

L4 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5

AN 1997:307225 BIOSIS
DN PREV199799615028
TI Atrial natriuretic peptide induces apoptosis in neonatal rat cardiac myocytes.
AU Wu, Can-Fang; Bishopric, Nanette H.; Pratt, Richard E. (1)
CS (1) Lab. Genet. Physiol., Cardiovas. Res., Thorn-12, Brigham and Women's Hosp., 75 Francis St., Boston, MA 02115 USA
SO Journal of Biological Chemistry, (1997) Vol. 272, No. 23, pp. 14860-14866. ISSN: 0021-9258.
DT Article
LA English
AB Early heart failure is characterized by elevated plasma atrial natriuretic peptide (ANP) levels, but little is known about the direct effects of ANP on cardiac myocytes. In neonatal rat cardiac myocytes, ANP induced apoptosis in a dose-dependent and cell type-specific manner. Maximum effects occurred at 1 mu-M ANP, with a 4-5-fold increase in apoptotic cells, reaching a maximum apoptotic index of 19%. In contrast, the maximum apoptotic index of ANP-treated non-myocytes was 1.1 +- 0.2%, equivalent to control cultures. ANP treatment also sharply reduced levels of Mcl-1 mRNA, a Bcl-2 homologue, coincident with the increase in the incidence of apoptosis. ANP induction of apoptosis was receptor-dependent and mediated by cyclic GMP: the effect was mimicked by 8-bromo-cGMP, a membrane-***permeable*** analog, and by sodium nitroprusside, an ***activator*** of ***soluble*** ***guanylyl*** ***cyclase*** , and was potentiated by a cGMP-specific phosphodiesterase inhibitor, zaprinast. Interestingly, norepinephrine, a myocyte growth factor, inhibited ANP-induced apoptosis via activation of the beta-adrenergic receptor and elevation of cyclic AMP. These results show that ANP is a specific effector of cardiac myocyte apoptosis in culture via receptormediated elevation of cGMP. Furthermore, at least in this model, ANP and norepinephrine may have opposing roles in the modulation of cardiac myocyte growth and survival.

L4 ANSWER 10 OF 16 MEDLINE DUPLICATE 6
AN 97259097 MEDLINE
DN 97259097 PubMed ID: 9105234
TI Inhaled nitric oxide pretreatment but not posttreatment attenuates ischemia-reperfusion-induced pulmonary microvascular leak.
AU Chetham P M; Sefton W D; Bridges J P; Stevens T; McMurtry I F
CS Department of Anesthesiology, University of Colorado Health Sciences Center, Denver 80262, USA.. paul.chetham@uchsc.edu
SO ANESTHESIOLOGY, (1997 Apr) 86 (4) 895-902. Journal code: 4SG; 1300217. ISSN: 0003-3022.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199705
ED Entered STN: 19970507
Last Updated on STN: 19970507
Entered Medline: 19970501
AB BACKGROUND: Ischemia-reperfusion (I/R) pulmonary edema probably reflects a
leukocyte-dependent, oxidant-mediated mechanism. Nitric oxide (NO) attenuates leukocyte-endothelial cell interactions and I/R-induced microvascular leak. Cyclic adenosine monophosphate (cAMP) agonists reverse and prevent I/R-induced microvascular leak, but reversal by inhaled NO (INO) has not been tested. In addition, the role of ***soluble*** ***guanylyl*** ***cyclase*** (sGC) ***activation*** in the NO protection effect is unknown. METHODS: Rat lungs perfused with salt solution were grouped as either I/R, I/R with INO (10 or 50 ppm) on reperfusion, or time control. Capillary filtration coefficients (Kfc) were estimated 25 min before ischemia (baseline) and after 30 and 75 min of reperfusion. Perfusate cell counts and lung homogenate myeloperoxidase activity were determined in selected groups. Additional groups were treated with either INO (50 ppm) or isoproterenol (ISO-10 microM) after 30 min of reperfusion. Guanylyl cyclase was inhibited with 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one (ODQ-15 microM), and Kfc was estimated at baseline and after 30 min of reperfusion. RESULTS: (1) Inhaled NO attenuated I/R-induced increases in Kfc. (2) Cell counts were similar at baseline. After 75 min of reperfusion, lung neutrophil retention (myeloperoxidase activity) and decreased perfusate neutrophil counts were similar in all groups. (3) In contrast to ISO, INO did not reverse microvascular leak. (4) 8-bromoguanosine 3',5'-cyclic monophosphate (8-br-cGMP) prevented I/R-induced microvascular leak in ODQ-treated lungs, but INO was no longer effective. CONCLUSIONS: Inhaled NO attenuates I/R-induced pulmonary microvascular leak, which requires sGC activation and may involve a mechanism independent of inhibition of leukocyte-endothelial cell interactions. In addition, INO is ineffective in reversing I/R-induced microvascular leak.

L4 ANSWER 11 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 1997:83716 BIOSIS
DN PREV199799375429
TI Evidence that potassium channels make a major contribution to SIN-1-evoked relaxation of rat isolated mesenteric artery.
AU Plane, Frances (1); Hurrell, Amber; Jeremy, Jamie Y.; Garland, Christopher J.
CS (1) Dep. Pharmacol., University Bristol, University Walk, Bristol BS8 1TD UK
SO British Journal of Pharmacology, (1996) Vol. 119, No. 8, pp. 1557-1562. ISSN: 0007-1188.
DT Article
LA English
AB 1. The NO donor 3-morpholino-sydnonimine (SIN-1; 0.01-10 mu-M) evoked concentration-dependent relaxation of rat isolated mesenteric arteries pre-constricted with phenylephrine (1-3 mu-M). The relaxation to SIN-1 was not significantly different between endothelium-intact or denuded arterial segments or segments in which basal nitric oxide (NO) synthesis was inhibited (n=8; P gt 0.05). In contrast, the membrane ***permeable*** analogue of guanosine 3': 5'-cyclic monophosphate (cyclic GMP), 8-Br-cyclic GMP (0.01-1 mM), was much less effective in relaxing intact than denuded arterial segments or intact arterial segments pre-incubated with NO synthase blockers (n = 4; P lt 0.01). 2. 1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one (ODQ; 10 mu-M; 10 min) alone, did not alter SIN-I-evoked relaxation in any tissues (n=5; P gt 0.05). However, in parallel experiments, ODQ almost completely inhibited both basal and SIN-1-stimulated production of cyclic GMP in both the presence and absence of NO synthase blockers (n = 6; P lt 0.01) indicating that full relaxation to SIN-1 can be achieved in the absence of an increase in cyclic GMP. 3. Exposure of endothelium-intact arterial segments to the potassium channel blocker charybdotoxin (50 nM; 10 min), significantly inhibited SIN-1-evoked relaxation, reducing the maximum response by around 90% (n = 5; P lt 0.01). In contrast, in arterial segments in which either the endothelial cell layer had been removed or basal NO synthesis inhibited, relaxation to SIN-1 was not reduced in the presence of charybdotoxin (n=6; P gt 0.05). However, in the presence of NO synthase blockers and L-arginine (300 mu-M) together, charybdotoxin did significantly inhibit SIN-1-evoked relaxation to a similar extent as intact tissues (maximum response reduced by around 80%; n=4; P lt 0.01). 4. Pre-incubation with apamin (30 nm; 10 min) or glibenclamide (10 mu-M; 10 min) did not alter SIN-1-evoked relaxation of phenylephrine-induced tone in any tissues (n=4 and n=6, respectively; P gt 0.05). However, in the presence of either ODQ and apamin, or ODQ and glibenclamide, SIN-1-evoked relaxation was significantly attenuated in intact arterial segments and segments in which NO synthesis was blocked. 5. Exposure of intact arterial segments to charybdotoxin and apamin, in the presence of NO synthase blockers, also significantly inhibited SIN-1-evoked relaxation, reducing the maximum response by around 80% (n=4; P lt 0.01). 6. Addition of superoxide dismutase (SOD; 30 u ml-1), potentiated relaxations to SIN-1 in all tissues, but did not alter the effects of charybdotoxin and ODQ on SIN-1-evoked relaxation. 7. These data show that although relaxation to the NO-donor SIN-1 is not significantly different between endothelium-intact and denuded arterial segments, the mechanisms which mediate SIN-1-evoked relaxation in the rat isolated mesenteric artery appear to be modulated by the basal release of endothelium-derived NO. In the presence of an intact endothelial cell layer, the major mechanism for SIN-1-evoked relaxation appears to be the activation of charybdotoxin-sensitive potassium channels. In contrast, when basal NO synthesis is inhibited, SIN-1 appears to cause full relaxation by both the activation of a charybdotoxin-sensitive pathway and the ***stimulation*** of ***soluble*** ***guanylyl*** ***cyclase*** .

L4 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1996:264245 BIOSIS
DN PREV199698820374
TI Functional antagonism between cAMP and cGMP on ***permeability*** of coronary endothelial monolayers.
AU Hempel, A.; Noll, T. (1); Muhs, A.; Piper, H. M.
CS (1) Physiologisches Inst., Justus-Liebig-Univ., Aulweg 129, D-35392 Giessen Germany
SO American Journal of Physiology, (1996) Vol. 270, No. 4 PART 2, pp. H1264-H1271. ISSN: 0002-9513.
DT Article
LA English
AB The role of the intracellular second messengers guanosine 3',5'-cyclic monophosphate (cGMP) and adenosine 3',5'-cyclic monophosphate (cAMP) in the control of macromolecule ***permeability*** was studied in cultured monolayers of microvascular coronary endothelial cells from rat. Macromolecule ***permeability*** was determined as passage of fluorescein isothiocyanate (FITC)-labeled albumin across the monolayers. Activation of adenylyl cyclase by the beta-adrenoceptor agonist isoproterenol (Iso; 10-5 M) and the A-2-adenosine receptor agonist 5'-(N-ethylcarboxamido)-adenosine (NECA; 10-7 M) induced an increase in cellular cAMP contents that was accompanied by an increase in albumin flux. Effects of Iso and NECA on cellular cAMP level and albumin flux could be antagonized by a stimulator of the particulate guanylyl cyclase, atrial natriuretic peptide (ANP; 10-7 M), and ***stimulators*** of the ***soluble*** ***guanylyl*** ***cyclase*** , 3-morpholinosydnonimine (SIN-1; 10-7 M) and sodium nitroprusside (SNP; 10-6 M). ANP, SIN-1, and SNP also reduced cAMP content and basal macromolecule
flux in unstimulated monolayers. 8-Bromoguanosine 3',5'-cyclic monophosphate (8-BrcGMP; 5 times 10-6 M), a stimulator of protein kinase G, reduced the increase in albumin flux under Iso (10-5 M), NECA (10-7 M), or 8-bromoadenosine 3',5'-cyclic monophosphate (8-BrcAMP; 5 times 10-6 M). The present study shows that cGMP and cAMP are functional antagonists in the control of macromolecule ***permeability*** .

L4 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 1996:104115 BIOSIS
DN PREV199698676250
TI Atrial natriuretic peptide induces the expression of MKP-1, a mitogen-activated protein kinase phosphatase, in glomerular mesangial cells.
AU Sugimoto, Toshiro; Haneda, Masakazu (1); Togawa, Masaki; Isono, Motohide; Shikano, Tsutomu; Araki, Shin-Ichi; Nakagawa, Takahiko; Kashiwagi, Atsunori; Guan, Kun-Liang; Kikkawa, Ryuichi
CS (1) Third Dep. Medicine, Shiga Univ. Med. Sci., Otsu, Shiga 520-21 Japan
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 1, pp. 544-547. ISSN: 0021-9258.
DT Article
LA English
AB Atrial natriuretic peptide (ANP) has been shown to inhibit the proliferation of various types of cells including glomerular mesangial cells. The activation of mitogen-activated protein kinase (MAPK) is one of the main signal transduction systems leading to cell proliferation. MAPK is tightly regulated by the activating kinase, MEK, and specific phosphatase MKP-1. Constitutive expression of MKP-1 has been shown to inhibit cell proliferation by suppressing MAPK activity. In order to understand the mechanism of the anti-proliferative effect of ANP, we examined whether ANP could inhibit MAPK by inducing MKP-1 in cultured rat glomerular mesangial cells. ANP increased the expression of MKP-1 mRNA in a dose-dependent (10 nM maximum) and time-dependent, with a peak stimulation at 30 min, manner. Receptor for ANP is a transmembrane guanylyl cyclase. Activation of guanylyl cyclase of ANP receptor by ligand plays an essential role in ANP signal transduction. 8-Bromo-cGMP, a cell ***permeable*** analogue of cyclic GMP, and sodium nitroprusside, an ***activator*** of ***soluble*** ***guanylyl*** ***cyclase*** , could mimic the effects of ANP and were able to induce the expression of MKP-1 in a similar time course as ANP. The protein expression of MYP-1 was maximally stimulated by ANP at 120 min. Treatment of the cells with ANP for 120 min resulted in an inhibition of phorbol ester-induced activation of MAPK, while the activation of MEK was not affected by ANP. These results indicate that ANP might inhibit the proliferation of mesangial cells by inactivating MAPK through the induction of MKP-1.

L4 ANSWER 14 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 1994:304843 BIOSIS
DN PREV199497317843
TI Nitric oxide and carbon monoxide as possible retrograde messengers in hippocampal long-term potentiation.
AU Hawkins, R. D. (1); Zhuo, M.; Arancio, O.
CS (1) Cent. Neurobiol. and Behavior, Coll. Physicians and Surgeons, Columbia Univ., New York, NY USA
SO Journal of Neurobiology, (1994) Vol. 25, No. 6, pp. 652-665. ISSN: 0022-3034.
DT General Review
LA English
AB We have been investigating the hypothesis that the membrane-permeant molecules nitric oxide (NO) and carbon monoxide (CO) may act as retrograde messengers during long-term potentiation (LTP). Inhibitors of either NO synthase or heme oxygenase, the enzyme that produces CO, blocked induction of LTP in the CA1 region of hippocampal slices. Brief application of either NO or CO to slices produced a rapid and long-lasting increase in the size of synaptic potentials if, and only if, the application occurred at the same time as weak tetanic stimulation of the presynaptic fibers. The long-term enhancement by NO or CO was spatially restricted to synapses from active presynaptic fibers and appeared to involve mechanisms utilized by LTP, occluding the subsequent induction of LTP by strong tetanic stimulation. The enhancement by NO or CO was not blocked by the NMDA receptor blocker APV, suggesting that NO and CO act downstream from the NMDA receptor. In other systems, both NO and CO produce many of their effects by ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** and cGMP-dependent protein kinase. An inhibitor of soluble guanylyl cyclase blocked the induction of normal LTP. Conversely, the membrane- ***permeable*** analog 8-Br-cGMP produced a rapid onset and long-lasting synaptic enhancement if, and only if, it was applied at the same time as weak presynaptic stimulation. Similarly, two inhibitors of cGMP-dependent protein kinase blocked the induction of normal LTP, and a selective activator of cGMP-dependent protein kinase produced activity-dependent long-lasting synaptic enhancement. 8-Br-cGMP also produced an activity-dependent, long-lasting increase in the amplitude of evoked synaptic currents between pairs of hippocampal neurons in dissociated cell culture. In addition, 8-Br-cGMP, like NO, produced a long-lasting increase in the frequency of spontaneous miniature synaptic currents. These results are consistent with the hypothesis that NO and CO, either alone or in combination, serve as retrograde messengers that produce activity-dependent presynaptic enhancement, perhaps by ***stimulating*** ***soluble*** ***guanylyl*** ***cyclase*** and cGMP-dependent protein kinase, during LTP in hippocampus.

L4 ANSWER 15 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 1994:409083 BIOSIS
DN PREV199497422083
TI New signaling mechanism of angiotensin II in neuroblastoma neuro-2A cells: ***Activation*** of ***soluble*** ***guanylyl*** ***cyclase*** via nitric oxide synthesis.
AU Chaki, Shigeyuki; Inagami, Tadashi (1)
CS (1) Dep. Biochemistry, Vanderbilt Univ. Sch. Med., Nashville, TN 37232-0146 USA
SO Molecular Pharmacology, (1993) Vol. 43, No. 4, pp. 603-608. ISSN: 0026-895X.
DT Article
LA English
AB We previously reported that angiotensin II (Ang II) increases cGMP content through a new Ang II receptor subtype that is distinct from both the AT-1 and AT-2 subtypes in differentiated Neuro-2A cells. In this study, the mechanism of the Ang II-stimulated cGMP increase was investigated in comparison with bradykinin- and atria) natriuretic factor (ANF)-stimulated cGMP increases in differentiated Neuro-2A cells. Ang II increased cGMP in differentiated Neuro-2A cells rapidly, with a maximal effect in 30 sec and a return to basal levels in 60 sec. Removal of extracellular Ca-2+ or pretreatment with a membrane- ***permeable*** Ca-2+ chelator (1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetraacetoxymethyl ester) attenuated Ang II-stimulated cGMP accumulation. Both the time course and Ca-2+ dependency of the effect of Ang II were similar to those of the effect of bradykinin, which ***activates*** ***soluble*** ***guanylyl*** ***cyclase*** , but distinct from those of the effect of ANF, which activates particulate guanylyl cyclase. Methylene blue, an inhibitor of soluble guanylyl cyclase, attenuated the effects of Ang II and bradykinin but not that of ANF. LaCl-3, a nonspecific Ca-2+ blocker, prevented Ang II-stimulated cGMP accumulation. L-type Ca-2+ channel blockers, nifedipine and diltiazem, or an N-type Ca-2+ channel blocker, omega-conotoxin, failed to inhibit the effect of Ang II. Ang II had no effect on formation of 1,4,5-inositol trisphosphate or cAMP content, whereas bradykinin stimulated 1,4,5-inositol trisphosphate formation in differentiated Neuro-2A cells. Further, the nitric oxide synthase inhibitors N-G-monomethyl-L-arginine and N-G-nitro-L-arginine attenuated Ang II- and bradykinin-stimulated elevation of cGMP content but not that stimulated by ANF. The Ca-2+ ionophore A23187 also stimulated cGMP formation and the effect was inhibited by the nitric oxide synthase inhibitors. These results indicate that the newly found Ang II receptor mediates cGMP formation through ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** and that the ***activation*** is mediated by nitric oxide, which is increased by Ca-2+ influx via an ion channel distinct from the L-type and N-type Ca-2+ channels.

L4 ANSWER 16 OF 16 MEDLINE DUPLICATE 12
AN 91110530 MEDLINE
DN 91110530 PubMed ID: 1703296
TI Purification of a soluble isoform of guanylyl cyclase-activating-factor synthase.
AU Schmidt H H; Pollock J S; Nakane M; Gorsky L D; Forstermann U; Murad F
CS Abbott Laboratories, Abbott Park, IL 60064-3500.
NC AR 08080 (NIAMS)
DK30787 (NIDDK)
HL 28474 (NHLBI)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
AMERICA, (1991 Jan 15) 88 (2) 365-9.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199102
ED Entered STN: 19910329
Last Updated on STN: 19970203
Entered Medline: 19910228
AB The soluble form of guanylyl cyclase-activating-factor (GAF) synthase from rat cerebellum was purified to homogeneity by sequential affinity chromatographic steps on adenosine 2',5'-bisphosphate (2',5'-ADP)-Sepharose and calmodulin-agarose. Enzyme activity during purification was bioassayed by the L-arginine-, NADPH-, and Ca2+/calmodulin-dependent formation of a plasma membrane- ***permeable*** nitric oxide-like factor that ***stimulated*** ***soluble*** ***guanylyl*** ***cyclase*** in RFL-6 cells. With calmodulin and NADPH as cofactors, purified soluble GAF synthase induced an increase of 1.05 mumol of cGMP per 10(6) RFL-6 cells per 3 min per mg of protein. The coproduct of this signal-transduction pathway appeared to be L-citrulline. GAF synthase catalyzed the conversion of 107 nmol of L-arginine into L-citrulline per min per mg of protein. Based on these assays, this represents a purification of GAF synthase of approximately 10,076- and 8925-fold with recoveries of 16% and 19%, respectively. Rechromatography of the purified enzyme on Mono P (isoelectric point = 6.1 +/- 0.3), Mono Q, and Superose 12 or 6 resulted in no further purification or increase in specific activity. A Stokes radius of 7.9 +/- 0.3 nm and a sedimentation coefficient s20,w of 7.8 +/- 0.2 S were used to calculate a molecular mass of about 279 +/- 25 kDa for the native enzyme. SDS/PAGE revealed a single protein band with a molecular mass of about 155 +/- 3 kDa. These data suggest that soluble GAF synthase purified from rat cerebellum is a homodimer of 155-kDa subunits and that enzyme activity is dependent upon the presence of calmodulin.

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NEWS 4 Feb 01 DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5 Feb 19 Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6 Mar 08 Gene Names now available in BIOSIS
NEWS 7 Mar 22 TOXLIT no longer available
NEWS 8 Mar 22 TRCTHERMO no longer available
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=> s potassium channel activator (3s) (tumor or glioma or cancer)
L1 5 POTASSIUM CHANNEL ACTIVATOR (3S) (TUMOR OR GLIOMA OR CANCER)

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L2 2 DUP REM L1 (3 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L2 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 1999:188149 BIOSIS
DN PREV199900188149
TI Membrane potential and resistance changes in NG108-15 cells: An in vitro model to study membrane-active compounds.
AU Doebler, Jeffrey A. (1)
CS (1) Neurotoxicology Branch, Pharmacology Division, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Aberdeen, MD, 21010 USA
SO Toxicology Methods, (Jan.-March, 1999) Vol. 9, No. 1, pp. 35-45. ISSN: 1051-7235.
DT Article
LA English
AB The objective of this work was to develop an in vitro model to screen possible antidotal treatments against membrane-active compounds. Toward this end, studies were conducted to examine changes in membrane potential and resistance induced by several test compounds, i.e., gramicidin D, ouabain, and minoxidil, in differentiated NG108-15 hybrid (mouse neuroblastoma X rat ***glioma***) cells using intracellular electrodes and standard current clamp techniques. In general, changes observed were consistent with known actions of these compounds and their effects demonstrated in a number of other systems. For example, the channel-forming ionophore gramicidin D produced severe membrane depolarization with markedly reduced resistance. Also, the Na+-K+ pump blocker ouabain produced membrane depolarization, and the ***potassium*** ***channel*** ***activator*** minoxidil produced membrane hyperpolarization. Neither ouabain nor minoxidil significantly altered input resistance of the NG108-15 cells. The nature of the observed alterations combined with the consistency apparent in concentration-response profiles suggests that this model system is suitable for screening the effects of possible antidotal treatments against these and other membrane-active compounds.

L2 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 1992:403206 BIOSIS
DN BR43:59081
TI ALTERATIONS IN MACROPHAGE FREE RADICAL AND ***TUMOR*** NECROSIS FACTOR PRODUCTION BY A ***POTASSIUM*** ***CHANNEL*** ***ACTIVATOR*** .
AU POGREBNIAK H W; MATTHEWS W; PASS H I
CS THORACIC ONCOLOGY SECTION, SURGERY BRANCH, NATIONAL CANCER INST., NATIONAL INST. HEALTH, BETHESDA, MD. 20892.
SO ANNUAL MEETING OF THE ASSOCIATION FOR ACADEMIC SURGERY, COLORADO SPRINGS, COLORADO, USA, NOVEMBER 20-23, 1991. J SURG RES. (1992) 52 (4), 395-400. CODEN: JSGRA2. ISSN: 0022-4804.
DT Conference
FS BR; OLD
LA English

=> s (activat? or stimulat?) (3a) soluble guanylyl cyclase
L3 749 (ACTIVAT? OR STIMULAT?) (3A) SOLUBLE GUANYLYL CYCLASE

=> s l3 and review
L4 20 L3 AND REVIEW

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 16 DUP REM L4 (4 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 16 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 16 MEDLINE DUPLICATE 1
AN 2002165350 IN-PROCESS
DN 21895301 PubMed ID: 11897489
TI Nitric oxide and the other cyclic nucleotide.
AU Klein Claudette
CS E.A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University Medical School, 1402 South Grand Boulevard, 63104, St. Louis, MO, USA.
SO CELLULAR SIGNALLING, (2002 Jun) 14 (6) 493-8. Journal code: 8904683. ISSN: 0898-6568.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020319
Last Updated on STN: 20020319
AB Nitric oxide (NO) participates in the regulation of the daily activities of cells as well as in cytotoxic events. Elucidating the mechanism(s) by which NO carries out its diverse functions has been the goal of numerous laboratories. In the cardiovascular system, evidence indicates that NO mediates its effects via an ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** (sGC). In other tissues, it is not

clear if sGC is an exclusive target for NO or what the functions of cGMP might be. It is also unlikely that the diversity of NO actions is explained solely by changes in cGMP. This ***review*** focuses on the evidence that NO modulates cAMP signalling, with specific attention to the effects of NO on adenylyl cyclase (AC) as the target of NO regulation.

L5 ANSWER 2 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:158440 BIOSIS
DN PREV200200158440
TI Nitric oxide: One of the more conserved and widespread signaling molecules.
AU Torreilles, Jean (1)
CS (1) Defense et Resistance des Invertebres Marins, IFR 56 "Eugene Bataillon", UMR 5098, Universite Montpellier II, cp 80, 2 place Eugene Bataillon, 34095, Montpellier Cedex 5: jtorreil@univ-montp2.fr France
SO Frontiers in Bioscience, (Oct 1, 2001) Vol. 6, No. Cited Dec 4, 2001, pp. d1161-1172. http://www.bioscience.org/2001/v6/d/torreill/fulltext.htm cited December 19, 2001 http://www.bioscience.org/. online.
DT General Review
LA English
AB After the discovery of the vasodilatory functions of nitric oxide (NO), many signaling mechanisms involving NO were identified through experiments on mammals. NO ***activates*** ***soluble*** ***guanylyl*** ***cyclase*** to induce the formation of cGMP, stimulates ADP-ribosylation of GAPDH to alter cell energy production, and combines with superoxide to generate peroxynitrite. It then became clear that NO was a major messenger molecule in mammals, involved in the regulation of blood vessel dilatation, immune function and neurotransmission in the brain and peripheral nervous system. The wide spectrum of physiological effects of NO in mammals prompted researchers to look for the presence of NO in vertebrates and invertebrates. Parallel findings on the presence of NO signaling in vertebrates and invertebrates were observed, and then NO was found to be a signaling molecule widely spread throughout the metazoan kingdom and whose functions were highly conserved during evolution. These features were extended to the entire animal kingdom after the discovery of NOS activity in protozoa, yeasts and bacteria. Recently, the involvement of NO and NOS in plant disease resistance to infection was documented and many close similarities were detected between NO-dependent signaling mechanisms involved in plants and those identified in animals. All of these results indicated that NO is one of the earliest and most widespread signaling molecules in living organisms. This short ***review*** was aimed at marshalling recent information that led to this conclusion.

L5 ANSWER 3 OF 16 MEDLINE
AN 2002206065 IN-PROCESS
DN 21936852 PubMed ID: 11938558
TI [In Process Citation].
Les apports de l'etude des invertebres a la biologie du monoxyde d'azote.
AU Torreilles J; Guerin M C
CS UMR 5098, Defense et Resistance des Invertebres Marins, Universite Montpellier II, cp 80, 2, place Eugene Bataillon, 34095-Montpellier, France.
SO JOURNAL DE LA SOCIETE DE BIOLOGIE, (2001) 195 (4) 413-7. Journal code: 100890617.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020410
Last Updated on STN: 20020410
AB After the identification of nitric oxide (NO) with the endothelium derived-relaxing factor, many signaling mechanisms involving NO were identified through experiments on Mammals. NO ***activates*** ***soluble*** ***guanylyl*** ***cyclase*** leading to the formation of cGMP, stimulates the ADP-ribosylation of GAPDH, altering the cell energy production and combines with superoxide, generating cytotoxic peroxynitrite. NO was then progressively established as a major messenger molecule in Mammals. It is implied in the regulation of blood vessel dilatation, immune function, development and neurotransmission in brain and peripheral nervous system. Later, parallel findings were observed in Invertebrates and then, NO appeared as a signaling molecule widely spread throughout the animal kingdom and whose functions were highly conserved during evolution. The purpose of this short ***review*** is to highlight the contribution of Invertebrate studies to the knowledge of NO biology.

L5 ANSWER 4 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2001:204078 BIOSIS
DN PREV200100204078
TI Sources and targets of nitric oxide signalling in insect nervous systems.
AU Bicker, Gerd (1)
CS (1) Institut fuer Tieroekologie und Zellbiologie, Tieraerztliche Hochschule Hannover, Buenteweg 17d, 30559, Hannover: gbicker@zellbiologie.tiho-hannover.de Germany
SO Cell & Tissue Research, (February, 2001) Vol. 303, No. 2, pp. 137-146. print.
ISSN: 0302-766X.
DT Article
LA English
SL English
AB Nitric oxide (NO) is a membrane permeant signalling molecule which ***activates*** ***soluble*** ***guanylyl*** ***cyclase*** and leads to the formation of cyclic GMP (cGMP) in target cells. In the nervous system, NO/cGMP signalling is thought to play essential roles in synaptic plasticity during development and also in the mature animal. This ***review*** summarizes neurochemical, cell biological, and physiological investigations of NO/cGMP signalling in the nervous system of insects. The anatomical localization of donor and target cells suggests functions in olfaction, vision, and mechanosensation. Behavioural assays have uncovered contributions of NO signalling in oxygen sensing, habituation to chemosensory stimuli, and associative memory formation. During development, NO regulates cell proliferation, axonal outgrowth, and synaptic maturation. The cellular distribution of NO-responsive cells suggests that NO can serve as a retrograde synaptic messenger, as an intracellular messenger, and as a lateral diffusible messenger irrespective of conventional synaptic connectivity.

L5 ANSWER 5 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000359768 EMBASE
TI Molecular actions of nitric oxide in mesangial cells.
AU Sandau K.B.; Brune B.
CS B. Brune, University of Erlangen-Nurnberg, Faculty of Medicine, Loschgestrasse 8, 91054 Erlangen, Germany. mfm423@rzmail.uni-erlangen.de
SO Histology and Histopathology, (2000) 15/4 (1151-1158).
Refs: 54
ISSN: 0213-3911 CODEN: HIHIES
CY Spain
DT Journal; General Review
FS 029 Clinical Biochemistry
030 Pharmacology
028 Urology and Nephrology
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LA English
SL English
AB Nitric oxide (NO) is a widely recognized mediator of physiological and pathophysiological signal transmission. Its generation through L-arginine metabolism is relevant in the mesangium of the kidney where NO is produced by constitutive and inducible NO-synthase isoenzymes. Signaling is achieved through target interactions via redox and additive chemistry. In mesangial cells (MC), the outcome of these modifications promote on one side ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** while on the other side cytotoxicity is elicited. These contrasting situations are characterized by: 1) cGMP formation and signal propagation towards myosin light chain kinase, the effector system that regulates F-actin assembly, thereby affecting reversible relaxation/contraction of mesangial cells; and 2) initiation of morphological and biochemical alterations that are reminiscent of apoptosis such as chromatin condensation, p53 or Bax accumulation as well as caspase-3 activation. Off note, NO formation with concomitant initiation of apoptosis is efficiently antagonized by the simultaneous presence of superoxide (O_2^-). We will recall the consequences that stem from a diffusion controlled NO/O_2^- interaction thereby redirecting the apoptotic initiating activity of either NO or O_2^- towards protection. The crosstalk between cell destructive and protective signaling pathways, their activation or inhibition under the modulatory influence of NO will be discussed. Here we give examples of how NO elicits physiological and pathophysiological signal transmission in rat MC.

L5 ANSWER 6 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000017503 EMBASE
TI Studying the structure and regulation of soluble guanylyl cyclase.
AU Koesling D.
CS D. Koesling, Institut fur Pharmakologie, Freie Universitat Berlin, Thielallee 67-73, D-14195 Berlin, Germany
SO Methods: A Companion to Methods in Enzymology, (1999) 19/4 (485-493).
Refs: 51
ISSN: 1046-2023 CODEN: MTHDE
CY United States
DT Journal; General Review
FS 029 Clinical Biochemistry
LA English
SL English
AB Soluble guanylyl cyclase acts as the receptor for the signaling molecule nitric oxide. The enzyme consists of two different subunits. Each subunit shows the cyclase catalytic domain, which is also conserved in the membrane-bound guanylyl cyclases and the adenylyl cyclases. The N-terminal regions of the subunits are responsible for binding of the prosthetic heme group of the enzyme, which is required for the stimulatory effect of nitric oxide (NO). The five-coordinated ferrous heme displays a histidine as the axial ligand; ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** by NO is initiated by binding of NO to the heme iron and proceeds via breaking of the histidine-to-iron bond. Recently, a novel pharmacological and possibly physiological principle of guanylyl cyclase sensitization was demonstrated. The substance YC-1 has been shown to activate the enzyme independent of NO, to potentiate the effect of submaximally effective NO concentrations, and to turn carbon monoxide into an effective ***activator*** of ***soluble*** ***guanylyl*** ***cyclase*** .

L5 ANSWER 7 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999432623 EMBASE

TI Nitric oxide in the lungtherapeutic and cellular mechanisms of action.
AU Weinberger B.; Heck D.E.; Laskin D.L.; Laskin J.D.
CS B. Weinberger, Dept. Pediatrics-Neonatology, UMDNJ-Robert Wood Johnson, Medical School, 254 Eastern Avenue, New Brunswick, NJ 08903, United States. barryw@pol.net
SO Pharmacology and Therapeutics, (1999) 84/3 (401-411).
Refs: 94
ISSN: 0163-7258 CODEN: PHTHDT
PUI S 0163-7258(99)00044-3
CY United States
DT Journal; General Review
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
002 Physiology
029 Clinical Biochemistry
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
LA English
SL English
AB Nitric oxide is produced by many cell types in the lung and plays an important physiologic role in the regulation of pulmonary vasomotor tone by several known mechanisms. Nitric oxide ***stimulates*** ***soluble*** ***guanylyl*** ***cyclase*** , resulting in increased levels of cyclic GMP in lung smooth muscle cells. The gating of K+ and Ca2+ channels by cyclic GMP binding is thought to play a role in nitric oxide-mediated vasodilation. Nitric oxide may also regulate pulmonary vasodilation by direct activation of K+ channels or by modulating the expression and activity of angiotensin II receptors. Administration of nitric oxide by inhalation has been shown to acutely improve hypoxemia associated with pulmonary hypertension in humans and animals. This is presumably due to its ability to induce pulmonary vasodilation. Inhaled nitric oxide improves oxygenation and reduces the need for extracorporeal membrane oxygenation in term and near-term infants with persistent pulmonary hypertension. However, long-term benefits to these infants have been difficult to demonstrate. In other pathologic conditions, such as prematurity and acute respiratory distress syndrome, short-term benefits have not been shown conclusively to outweigh potential toxicities. For example, high-dose inhaled nitric oxide decreases surfactant function in the lung. Inhaled nitric oxide also acts as a pulmonary irritant, causing priming of lung macrophages and oxidative damage to lung epithelial cells. Conversely, protective effects of nitric oxide have been described in a number of pathological states, including hyperoxic and ischemia/reperfusion injury. Nitric oxide has also been reported to protect against oxidative damage induced by other reactive intermediates, including superoxide anion and hydroxyl radical. The dose and timing of nitric oxide administration needs to be ascertained in clinical trials before recommendations can be made regarding its optimal use in patients. Copyright (C) 1999 Elsevier Science Inc.

L5 ANSWER 8 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998318676 EMBASE
TI Nitric oxide and hemoglobin.
AU Yonetani T.
CS T. Yonetani, Dept. of Biochemistry/Biophysics, Univ. of Pennsylvania Medical Center, Philadelphia, PA 19104-6089, United States
SO Folia Pharmacologica Japonica, (1998) 112/3 (155-160).
Refs: 15
ISSN: 0015-5691 CODEN: NYKZAU
CY Japan
DT Journal; General Review
FS 029 Clinical Biochemistry
LA Japanese
SL English; Japanese
AB Nitric oxide (NO) is produced by nitric oxide synthases (cNOS and iNOS) in endothelial cells upon stimulating by various agents like Ca2+-calmodulin, cytokines and TNF. It acts as a paracrine on adjacent cells to ***activate*** ***soluble*** ***guanylyl*** ***cyclase*** in the production of cGMP, a second messenger in signal transduction cascades, leading to various cellular responses. The circulating blood contains certain steady-state concentrations of NO in the plasma in order to maintain normal vascular tone and other appropriate conditions for the systematic and pulmonary circulation. This homeostasis of NO in the rapidly moving blood must be maintained by a delicate balance between its production by NOSs and its instant scavenging by hemoglobin (Hb) in the erythrocytes. Under physiological conditions ([NO] <<< [Hb]), NO is sequestered by deoxy Hb to form .alpha.-nitrosyl Hb, .alpha. (Fe-NO)2, .beta. (Fe)2 where NO is tightly (K(D) .noteq. 10-12 M) bound to the .alpha.-subunits. Upon binding NO to the .alpha.-subunits, Hb shifts its conformation to a T-(low- affinity extreme) state and its .beta.-subunits become an efficient O2 carrier. The same molecular mechanisms of NO-induced conformation change operates in both Hb and soluble guanylyl cyclase. This is caused by the NO-induced trans- axial cleavage of the heme Fe-proximal His bonds in these hemoproteins. This bond cleavage mechanism allows Hb to survive as an effective O2 carrier even after sequestration of NO. The NO sequestered in Hb is eventually oxidized aerobically to NO3- in the reaction of Fe-NO + O2 .fwdarw. Fe+ + NO3- . Met Hb (Fe+) so formed is cycled back to deoxy Hb (Fe) by intra-erythrocyte Hb reductase to complete the NO scavenging. Thus, to increase blood delivery, whereas excess NO in the blood, which is sequestered by Hb, could help Hb to deliver O2 more efficiently in peripheral tissues.

L5 ANSWER 9 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998146535 EMBASE
TI Resurgence of carbon monoxide: An endogenous gaseous vasorelaxing factor.
AU Wang R.
CS R. Wang, Department of Physiology, College of Medicine, University of Saskatchewan, 107 Wiggins Road, Saskatoon, Sask. S7N SE5, Canada
SO Canadian Journal of Physiology and Pharmacology, (1998) 76/1 (1-15).
Refs: 101
ISSN: 0008-4212 CODEN: CJPPA3
CY Canada
DT Journal; General Review
FS 002 Physiology
005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LA English
SL English; French
AB Carbon monoxide (CO) is an endogenously generated gas that may play an important physiological role in the regulation of vascular tone. The CO-induced vasorelaxation, as a result of a direct action on vascular smooth muscles, has been demonstrated in many cases. Three major cellular mechanisms are proposed to explain the vasorelaxing effect of CO. These include the ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** , ***stimulation*** of various types of K channels, and inhibition of the cytochrome P450 dependent monooxygenase system in vascular smooth muscle cells. An interaction between CO and nitric oxide may also significantly contribute to the fine tuning of vascular tone. Furthermore, alterations in either the endogenous production of CO or the vascular responsiveness to CO have been encountered in several pathophysiological situations. A better understanding of the vascular effects of CO and the underlying cellular and molecular mechanisms will pave the way for the establishment of the role played by CO in vascular physiology and pathophysiology.

L5 ANSWER 10 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998169005 EMBASE
TI The role of carbon monoxide in the regulation of neuroendocrine function.
AU Mancuso C.; Preziosi P.; Grossman A.B.; Navarra P.
CS Prof. P. Navarra, Institute of Pharmacology, Catholic Univ. School of Medicine, Largo Francesco Vito, I-00168 Rome, Italy. pnavarra@rm.unicatt.it
SO NeuroImmunoModulation, (1997) 4/5-6 (225-229).
Refs: 44
ISSN: 1021-7401 CODEN: NROIEM
CY Switzerland
DT Journal; General Review
FS 002 Physiology
003 Endocrinology
008 Neurology and Neurosurgery
LA English
SL English
AB This paper discusses the current evidence supporting the notion that endogenous carbon monoxide (CO) is a modulator of neuroendocrine function. CO is normally formed in the body during the enzymatic catabolism of heme moieties by heme oxygenase (HO). Three HO isoforms have been described to date: HO-1, HO-2 and HO-3. In the brain, CO is principally generated by HO-2 but, in discrete brain areas such as the paraventricular nuclei of the hypothalamus, a role for HO-1 is also possible. Moreover, under pathological conditions, the latter isoform is expressed by activated glial cells. The possible contribution by the recently described HO-3 remains to be established. Once formed, CO exerts its biological effects mainly via the ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** , but alternative signaling mechanisms, such as the activation of cyclo-oxygenase or the inhibition of cytochrome P450, have also been reported. In vitro studies, the formation of CO within the hypothalamus has been associated with inhibition of the release of hormones such as corticotropin-releasing hormone, arginine vasopressin and oxytocin involved in hypothalamo-pituitary-adrenal axis activation and, conversely, with stimulation of luteinising hormone-releasing hormone release, thus suggesting that the gas may have a neuroendocrine role which may be to prevent over-exuberant activation of the hypothalamo-pituitary-adrenal axis and inhibition of reproductive processes within the hypothalamus during stress. At present, however, the possible pathophysiological relevance of the in vitro observations remains to be demonstrated.

L5 ANSWER 11 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96191945 EMBASE
DN 1996191945
TI [Nitric oxide: An endothelium-derived local vascular nitrovasodilator system].
STICKSTOFFMONOXID: DAS ENDOGENE NITRAT IM KREISLAUF.
AU Tschudi M.R.; Luscher T.F.
CS Kardiologische Abteilung, Medizinische Universitatsklinik, Inselspital,CH-3010 Bern, Switzerland
SO Herz, (1996) 21/SUPPL. 1 (50-60).
ISSN: 0340-9937 CODEN: HERZDW
CY Germany
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA German

SL English; German
AB The endothelium takes part in the regulation of vascular tone through the production of endothelium-derived relaxing and contracting factors. The L-arginine pathway within endothelial cells in the blood vessel wall is the source of production of the endogenous nitrovasodilator, nitric oxide (NO). The NO molecule has one unpaired electron and readily reacts with oxygen, superoxide radicals, or transition metals. Therefore the measurement of the concentration of NO in biological systems is a challenging analytical problem. NO is formed from L-arginine via constitutive NO synthase. It is released under basal conditions and in response to mechanical stimuli such as shear stress and in response to receptor-operated agonists such as bradykinin, serotonin, ADP/ATP, thrombin, histamine and substance P. NO is the mediator of endothelium-dependent relaxation in the circulation and exerts its effects by ***activating*** ***soluble*** ***guanylyl*** ***cyclase*** in vascular smooth muscle, which in turn leads to the formation of cyclic guanosine monophosphate (cyclic GMP) and to relaxation. In addition to its effects on vascular smooth muscle, NO is also released abluminally to interact with circulating platelets. Increases in cyclic GMP in platelets are associated with a decreased adhesion and aggregation. In endothelial cells, NO inhibits its own production as well as that of the vasoconstrictor peptide endothelin-1. Thus, endothelium-derived NO, through its vasodilator and anti-aggregatory properties, prevents vasospasm and thrombus formation in the circulation and thereby helps to maintain blood flow to vital organs such as the heart. Under certain conditions such as inflammation, NO may also be formed via inducible nitric oxide synthase by smooth muscle cells, endothelium and monocytes. Therapeutic nitrates also exert their effects by releasing NO from their molecules and ***activating*** ***soluble*** ***guanylyl*** ***cyclase*** . Their effects are particularly pronounced in arteries in which the release of NO is inhibited or impaired or in the absence of the endothelium. Thus, the endothelial L-arginine pathway plays an important protective role in the local regulation of blood flow and through its vasodilator and antiplatelet properties. Nitrates can at least in part substitute the endogenous nitrovasodilator in disease states with impaired formation of NO.

L5 ANSWER 12 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94160109 EMBASE
DN 1994160109
TI Nitric oxide and carbon monoxide as possible retrograde messengers in hippocampal long-term potentiation.
AU Hawkins R.D.; Zhuo M.; Arancio O.
CS Center for Neurobiology and Behavior, College of Physicians and Surgeons, Columbia University,New York, NY 10032, United States
SO Journal of Neurobiology, (1994) 25/6 (652-665).
ISSN: 0022-3034 CODEN: JNEUBZ
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English
AB We have been investigating the hypothesis that the membrane-permeant molecules nitric oxide (NO) and carbon monoxide (CO) may act as retrograde messengers during long-term potentiation (LTP). Inhibitors of either NO synthase or heme oxygenase, the enzyme that produces CO, blocked induction of LTP in the CA1 region of hippocampal slices. Brief application of either NO or CO to slices produced a rapid and long-lasting increase in the size of synaptic potentials if, and only if, the application occurred at the same time as weak tetanic stimulation of the presynaptic fibers. The long-term enhancement by NO or CO was spatially restricted to synapses from active presynaptic fibers and appeared to involve mechanisms utilized by LTP, occluding the subsequent induction of LTP by strong tetanic stimulation. The enhancement by NO or CO was not blocked by the NMDA receptor blocker APV, suggesting that NO and CO act downstream from the NMDA receptor. In other systems, both NO and CO produce many of their effects by ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** and cGMP-dependent protein kinase. An inhibitor of soluble guanylyl cyclase blocked the induction of normal LTP. Conversely, the membrane-permeable analog 8-Br-cGMP produced a rapid onset and long-lasting synaptic enhancement if, and only if, it was applied at the same time as weak presynaptic stimulation. Similarly, two inhibitors of cGMP-dependent protein kinase blocked the induction of normal LTP, and a selective activator of cGMP-dependent protein kinase produced activity-dependent long-lasting synaptic enhancement. 8-Br-cGMP also produced an activity-dependent, long- lasting increase in the amplitude of evoked synaptic currents between pairs of hippocampal neurons in dissociated cell culture. In addition, 8-Br-cGMP, like NO, produced a long-lasting increase in the frequency of spontaneous miniature synaptic currents. These results are consistent with the hypothesis that NO and CO, either alone or in combination, serve as retrograde messengers that produce activity-dependent presynaptic enhancement, perhaps by ***stimulating*** ***soluble*** ***guanylyl*** ***cyclase*** and cGMP-dependent protein kinase, during LTP in hippocampus.

L5 ANSWER 13 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94336689 EMBASE
DN 1994336689
TI Coronary vasomotor responses: Role of endothelium and nitrovasodilators.
AU Bassenge E.
CS Institute of Applied Physiology, Hermann Herder Str. 7,D-79104 Freiburg, Germany
SO Cardiovascular Drugs and Therapy, (1994) 8/4 (601-610).
ISSN: 0920-3206 CODEN: CDTHET
CY United States
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The endogenous nitrovasodilator endothelium-derived nitric oxide (EDNO) is continuously synthetized enzymatically by NO synthase from L-arginine and is released from endothelial cells. Enhanced, superimposed EDNO release can be stimulated by various local and circulating factors, such as bradykinin, ATP, etc., but also most importantly by viscous drag-induced shear stress of the bloodstream acting on the endothelial lining. Thus luminal release suppresses leukocyte adhesion (expression of adhesion molecules), platelet activation, platelet adhesion, and platelet aggregation, and abluminal release counteracts myogenic and neurogenic coronary constrictor tone, thereby increasing myocardial perfusion and dilating large coronary artery calibers. Thus endothelial impairment and denudation (hypercholesterolemia, atheromatosis, balloon catheter interventions) favor excessive constrictor tone and myocardial ischemia. Under these conditions EDNO can be supplemented by compounds (e.g., nitroglycerin, isosorbide dinitrate) converted by biological systems into NO. In addition, it can be supplemented by compounds that even spontaneously release NO (e.g., sydnonimines such as SIN-1 and sodium nitroprusside). EDNO and exogenously supplemented NO ***stimulate*** ***soluble*** ***guanylyl*** ***cyclase*** , increase cGMP levels, and bring about vascular relaxation, particularly in those still compliant sections in which EDNO production is impaired and cGMP levels are thus diminished. Exogenous nitrovasodilators are preferentially converted (in the presence of cysteine) enzymatically in large coronary arteries, improving coronary conductance, and in the venous bed (preload reduction), resulting in an improved O2 supply/demand ratio. During chronic, continuous application, neurohormonal counterregulation and diminished enzymatic biotransformation into NO may reduce their effectiveness, resulting in tolerance, particularly in the most sensitive vascular sections, such as veins and coronary arteries. This drawback can be overcome by applying spontaneously NO-releasing compounds, intermittent therapy, or intermittent interposition of other vasodilator principles.

L5 ANSWER 14 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 93220811 EMBASE
DN 1993220811
TI Molecular characteristics and enzymology of nitric oxide synthase and soluble guanylyl cyclase in the CNS.
AU Mayer B.
CS Inst Pharmekologie und Toxikologie, Universitat Graz, Universitatsplatz 2,A-8010 Graz, Austria
SO Seminars in the Neurosciences, (1993) 5/3 (197-205).
ISSN: 1044-5765 CODEN: SNEUEZ
CY United Kingdom
DT Journal; General Review
FS 002 Physiology
008 Neurology and Neurosurgery
029 Clinical Biochemistry
LA English
SL English
AB Excitatory neurotransmission in CNS is accompanied by the synthesis and release of nitric oxide, a messenger molecule which may be involved in cellular communication and signal transduction. As a potent ***activator*** of home-containing ***soluble*** ***guanylyl*** ***cyclase*** , NO is thought to exert most of its cellular actions through accumulation of cGMP. In the brain, NO is produced enzymically from L-arginine by a Ca2+/ calmodulin-dependent NO synthase which is stimulated by influx of Ca2+ through activated NMDA receptors. Biochemical characterization and molecular cloning revealed brain NO synthase as highly complex, NADPH-dependent oxidoreductase containing the reduced flavins FAD and FMN, heme and tetrahydrobiopterin as prosthetic groups. Neuronal NO synthase and soluble guanylyl cyclase activities may be modulated by a complex network of intracellular processes, suggesting a tight regulation of NO/cGMP-mediated signal transduction.

L5 ANSWER 15 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1992:474005 BIOSIS
DN BA94:105380
TI NITRIC OXIDE CARBON MONOXIDE HYDROXYL ENDOGENOUS ***SOLUBLE*** ***GUANYLYL*** ***CYCLASE*** - ***ACTIVATING*** FACTORS.
AU SCHMIDT H H H W
CS MEDIZIN. UNIVERSITAETSKLIN., KLIN. FORSCHERGRUPPE, JOSEF-SCHNEIDER STR. 2,
W-8700 WUERZBURG, GER.
SO FEBS (FED EUR BIOCHEM SOC) LETT, (1992) 307 (1), 102-107.
CODEN: FEBLAL. ISSN: 0014-5793.
FS BA; OLD
LA English
AB Several low molecular weight compounds are capable of ***activating*** ***soluble*** ***guanylyl*** ***cyclase*** . Recent evidence suggests that some of these are formed under physiological conditions: the nitric oxide radical, carbon monoxide and the hydroxyl radical. Thus,

multiple signal transduction pathways appear to exist that form a guanylyl cyclase activating factors and thereby regulate the intracellular cyclic guanosine 3',5'-monophosphate level.

L5 ANSWER 16 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 92020789 EMBASE
DN 1992020789
TI Guanylyl cyclases, a growing family of signal-transducing enzymes.
AU Koesling D.; Bohme E.; Schultz G.
CS Institut fur Pharmakologie, Freie Universitat Berlin,D-1000 Berlin 33, Germany
SO FASEB Journal, (1991) 5/13 (2785-2791).
ISSN: 0892-6638 CODEN: FAJOEC
CY United States
DT Journal; General Review
FS 029 Clinical Biochemistry
LA English
SL English
AB Guanylyl cyclases, which catalyze the formation of the intracellular signal molecule cyclic GMP from GTP, display structural features similar to other signal-transducing enzymes such as protein tyrosine-kinases and protein tyrosine-phosphatases. So far, three isoforms of mammalian membrane-bound guanylyl cyclases (GC-A, GC-B, GC-C), which are stimulated by either natriuretic peptides (GC-A, GC-B) or by the enterotoxin of Escherichia coli (GC-C), have been identified. These proteins belong to the group of receptor-linked enzymes, with different NH2-terminal extracellular receptor domains coupled to a common intracellular catalytic domain. In contrast to the membrane-bound enzymes, the heme-containing ***soluble*** ***guanylyl*** ***cyclase*** is ***stimulated*** by NO and NO-containing compounds and consists of two subunits (.alpha.1 and .beta.1). Both subunits contain the putative catalytic domain, which is conserved in the membrane-bound guanylyl cyclases and is found twice in adenylyl cyclases. Coexpression of the .alpha.1- and .beta.1-subunit is required to yield a catalytically active enzyme. Recently, another subunit of soluble guanylyl cyclase was identified and designated .beta.2, revealing heterogeneity among the subunits of soluble guanylyl cyclase. Thus, different enzyme subunits may be expressed in a tissue-specific manner, leading to the assembly of various heterodimeric enzyme forms. The implications concerning the physiological regulation of soluble guanylyl cyclase are not known, but different mechanisms of soluble enzyme activation may be due to heterogeneity among the subunits of soluble guanylyl cyclase.

=> d his

(FILE 'HOME' ENTERED AT 15:36:56 ON 24 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 15:37:07 ON 24 APR 2002
L1 5 S POTASSIUM CHANNEL ACTIVATOR (3S) (TUMOR OR GLIOMA OR CANCER)
L2 2 DUP REM L1 (3 DUPLICATES REMOVED)
L3 749 S (ACTIVAT? OR STIMULAT?) (3A) SOLUBLE GUANYLYL CYCLASE
L4 20 S L3 AND REVIEW
L5 16 DUP REM L4 (4 DUPLICATES REMOVED)

=> s potassium channel? or K+ channel?
'K+' NOT VALID HERE
'K+' NOT VALID HERE
'K+' NOT VALID HERE

=> s potassium channel? or K channel?
L6 68800 POTASSIUM CHANNEL? OR K CHANNEL?

=> s l6 and (tumor or cancer or glioma or infection or stroke or ischemia)
L7 5157 L6 AND (TUMOR OR CANCER OR GLIOMA OR INFECTION OR STROKE OR ISCHEMIA)

=> s l3 and l7
L8 4 L3 AND L7

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 3 DUP REM L8 (1 DUPLICATE REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L9 ANSWER 1 OF 3 MEDLINE
AN 2000460055 MEDLINE
DN 20344999 PubMed ID: 10884560
TI The mechanism of actions of 3-(5'-(hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1) on Ca(2+)-activated K(+) currents in GH(3) lactotrophs.
AU Wu S N; Hwang T; Teng C M; Li H F; Jan C R
CS Department of Medical Research and Education, Veterans General Hospital-Kaohsiung, 386, Ta-Chung 1st Road, Kaohsiung, Taiwan, ROC.. snwu@isca.vghks.gov.tw
SO NEUROPHARMACOLOGY, (2000 Jul 24) 39 (10) 1788-99.
Journal code: NZB; 0236217. ISSN: 0028-3908.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928
AB The effects of 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1), an ***activator*** of ***soluble*** ***guanylyl*** ***cyclase*** , on ionic currents have been assessed in rat pituitary GH(3) lactotrophs. In GH(3) cells bathed in normal Tyrode's solution, YC-1 (1 microM) reversibly suppressed the amplitude of the Ca(2+)-activated K(+) current (I(K(Ca))). YC-1 at a concentration above 10 microM produced a biphasic response in the amplitude of I(K(Ca)), i.e., an initial decrease followed by a sustained increase. When the pipette solutions were filled with high EGTA (10 mM), the YC-1-induced stimulatory effect on I(K(Ca)) was abolished. Over a similar concentration range, YC-1 also effectively inhibited the voltage-dependent K(+) current (I(K(V))) in GH(3) cells. The IC(50) value required for the inhibition of I(K(V)) by YC-1 was 1 microM. Unlike YC-1, 8-bromo cGMP did not inhibit I(K(Ca)). However, YC-1 (10 microM) did not affect the amplitude of L-type Ca(2+) current. In the cell-attached configuration, application of YC-1 (10 microM) to the bath did not change the single-channel conductance of the large-conductance Ca(2+)-activated K(+) (BK(Ca)) channels; however, it did increase the opening probability of BK(Ca) channels. In contrast, in the outside-out configuration, YC-1 (10 microM) significantly suppressed the opening probability of BK(Ca) channels. The present study shows dual effects of YC-1 on I(K(Ca)) in GH(3) cells. The YC-1-mediated stimulation of I(K(Ca)) may result from elevated cytosolic Ca(2+), whereas the inhibition of I(K(Ca)) and I(K(V)) by YC-1 appears to be direct and independent of the ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** . Caution thus needs to be used in attributing the YC-1-mediated response to the ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** .

L9 ANSWER 2 OF 3 MEDLINE DUPLICATE 1
AN 2000127603 MEDLINE
DN 20127603 PubMed ID: 10665837
TI Nitric oxide in the lung: therapeutic and cellular mechanisms of action.
AU Weinberger B; Heck D E; Laskin D L; Laskin J D
CS Department of Pediatrics-Neonatology, UMDNJ-Robert Wood Johnson Medical School, St. Peter's University Hospital, New Brunswick, NJ 08903, USA.. barryw@pol.net
NC ES03643 (NIEHS)
ES03647 (NIEHS)
ES05022 (NIEHS)
+
SO PHARMACOLOGY AND THERAPEUTICS, (1999 Dec) 84 (3) 401-11. Ref: 95
Journal code: P44; 7905840. ISSN: 0163-7258.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000217
AB Nitric oxide is produced by many cell types in the lung and plays an important physiologic role in the regulation of pulmonary vasomotor tone by several known mechanisms. Nitric oxide ***stimulates*** ***soluble*** ***guanylyl*** ***cyclase*** , resulting in increased levels of cyclic GMP in lung smooth muscle cells. The gating of K+ and Ca2+ channels by cyclic GMP binding is thought to play a role in nitric oxide-mediated vasodilation. Nitric oxide may also regulate pulmonary vasodilation by direct activation of ***K*** + ***channels*** or by modulating the expression and activity of angiotensin II receptors. Administration of nitric oxide by inhalation has been shown to acutely improve hypoxemia associated with pulmonary hypertension in humans and animals. This is presumably due to its ability to induce pulmonary vasodilation. Inhaled nitric oxide improves oxygenation and reduces the need for extracorporeal membrane oxygenation in term and near-term infants with persistent pulmonary hypertension. However, long-term benefits to these infants have been difficult to demonstrate. In other pathologic conditions, such as prematurity and acute respiratory distress syndrome, short-term benefits have not been shown conclusively to outweigh potential toxicities. For example, high-dose inhaled nitric oxide decreases surfactant function in the lung. Inhaled nitric oxide also acts as a pulmonary irritant, causing priming of lung macrophages and oxidative damage to lung epithelial cells. Conversely, protective effects of nitric oxide have been described in a number of pathological states, including hyperoxic and ***ischemia*** /reperfusion injury. Nitric oxide has also been reported to protect against oxidative damage induced by other reactive intermediates, including superoxide anion and hydroxyl radical. The dose and timing of nitric oxide administration needs to be ascertained in clinical trials before recommendations can be made regarding its optimal use in patients.

L9 ANSWER 3 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94205485 EMBASE
DN 1994205485

TI Long term increases in coronary arterial conductance during five day infusion of low dose nicorandil.
AU Bassenge E.; Fink B.; Sommer O.; Huckstorf C.
CS University of Freiburg, Department of Applied Physiology, Hermann-Herder-Strasse 7,D-79104 Freiburg, Germany
SO Cardiovascular Research, (1994) 28/6 (912-916). ISSN: 0008-6363 CODEN: CVREAU
CY United Kingdom
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Objective: The aim was to test the effects of nicorandil on coronary arterial conductance and on a possible development of tolerance or cross tolerance with glyceryl trinitrate during a 5 d continuous intravenous infusion of this hybrid molecule (consisting of a combination of ***potassium*** ***channel*** activation and simultaneous nitro-ester induced ***soluble*** ***guanylyl*** - ***cyclase*** ***activation***). Methods: Continuous intravenous infusions of nicorandil at 2.5 .mu.g .cntdot. kg-1 .cntdot. min-1 and 10 .mu.g .cntdot. kg-1 .cntdot. min-1 into conscious chronically instrumented dogs were carried out for 5 d using a special portable infusion system. Employing additional short term infusions, dose-response curves were obtained by giving nicorandil or glyceryl trinitrate at increasing dosages both in the preinfusion control state and 4 h after terminating the nicorandil infusion. Results: The 5 d infusion of 2.5 or 10.0 .mu.g .cntdot. kg-1 .cntdot. min-1 nicorandil resulted in a significant increase in large coronary artery diameter by 4.21(SEM 0.14)% or 9.20(0.28)%, respectively. At the lower dose no significant tolerance or cross tolerance with glyceryl trinitrate was observed. However, at the higher dose there was a shift of the dose-response curve of both nicorandil and glyceryl trinitrate to the right, indicating some tolerance. The smaller dose did not induce hypotension or reflex increase in heart rate, whereas the larger resulted in a 42(2.5)% increase in heart rate. Conclusions: A dose regimen of 2.5 .mu.g .cntdot. kg-1 .cntdot. min-1 continuously administered for 5 d is capable of inducing a significant increase in coronary arterial conductance which was well maintained over the whole infusion period. Thus nicorandil can exert a selective large coronary artery dilatation and may bring about a well maintained increase in epicardial coronray conductance, especially when applied as a low dose slow release preparation which circumvents hypotension and increase in heart rate.

=> d his

(FILE 'HOME' ENTERED AT 15:36:56 ON 24 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 15:37:07 ON 24 APR 2002
L1 5 S POTASSIUM CHANNEL ACTIVATOR (3S) (TUMOR OR GLIOMA OR CANCER)
L2 2 DUP REM L1 (3 DUPLICATES REMOVED)
L3 749 S (ACTIVAT? OR STIMULAT?) (3A) SOLUBLE GUANYLYL CYCLASE
L4 20 S L3 AND REVIEW
L5 16 DUP REM L4 (4 DUPLICATES REMOVED)
L6 68800 S POTASSIUM CHANNEL? OR K CHANNEL?
L7 5157 S L6 AND (TUMOR OR CANCER OR GLIOMA OR INFECTION OR STROKE OR
L8 4 S L3 AND L7
L9 3 DUP REM L8 (1 DUPLICATE REMOVED)

=> s l6 and (tumor or cancer or glioma)
L10 1522 L6 AND (TUMOR OR CANCER OR GLIOMA)

=> s l3 and l10
L11 1 L3 AND L10

=> d bib abs

L11 ANSWER 1 OF 1 MEDLINE
AN 2000460055 MEDLINE
DN 20344999 PubMed ID: 10884560
TI The mechanism of actions of 3-(5'-(hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1) on Ca(2+)-activated K(+) currents in GH(3) lactotrophs.
AU Wu S N; Hwang T; Teng C M; Li H F; Jan C R
CS Department of Medical Research and Education, Veterans General Hospital-Kaohsiung, 386, Ta-Chung 1st Road, Kaohsiung, Taiwan, ROC.. snwu@isca.vghks.gov.tw
SO NEUROPHARMACOLOGY, (2000 Jul 24) 39 (10) 1788-99. Journal code: NZB; 0236217. ISSN: 0028-3908.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928
AB The effects of 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1), an ***activator*** of ***soluble*** ***guanylyl*** ***cyclase*** , on ionic currents have been assessed in rat pituitary GH(3) lactotrophs. In GH(3) cells bathed in normal Tyrode's solution, YC-1 (1 microM) reversibly suppressed the amplitude of the Ca(2+)-activated K(+) current (I(K(Ca))). YC-1 at a concentration above 10 microM produced a biphasic response in the amplitude of I(K(Ca)), i.e., an initial decrease followed by a sustained increase. When the pipette solutions were filled with high EGTA (10 mM), the YC-1-induced stimulatory effect on I(K(Ca)) was abolished. Over a similar concentration range, YC-1 also effectively inhibited the voltage-dependent K(+) current (I(K(V))) in GH(3) cells. The IC(50) value required for the inhibition of I(K(V)) by YC-1 was 1 microM. Unlike YC-1, 8-bromo cGMP did not inhibit I(K(Ca)). However, YC-1 (10 microM) did not affect the amplitude of L-type Ca(2+) current. In the cell-attached configuration, application of YC-1 (10 microM) to the bath did not change the single-channel conductance of the large-conductance Ca(2+)-activated K(+) (BK(Ca)) channels; however, it did increase the opening probability of BK(Ca) channels. In contrast, in the outside-out configuration, YC-1 (10 microM) significantly suppressed the opening probability of BK(Ca) channels. The present study shows dual effects of YC-1 on I(K(Ca)) in GH(3) cells. The YC-1-mediated stimulation of I(K(Ca)) may result from elevated cytosolic Ca(2+), whereas the inhibition of I(K(Ca)) and I(K(V)) by YC-1 appears to be direct and independent of the ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** . Caution thus needs to be used in attributing the YC-1-mediated response to the ***activation*** of ***soluble*** ***guanylyl*** ***cyclase*** .

=> d his

(FILE 'HOME' ENTERED AT 15:36:56 ON 24 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 15:37:07 ON 24 APR 2002
L1 5 S POTASSIUM CHANNEL ACTIVATOR (3S) (TUMOR OR GLIOMA OR CANCER)
L2 2 DUP REM L1 (3 DUPLICATES REMOVED)
L3 749 S (ACTIVAT? OR STIMULAT?) (3A) SOLUBLE GUANYLYL CYCLASE
L4 20 S L3 AND REVIEW
L5 16 DUP REM L4 (4 DUPLICATES REMOVED)
L6 68800 S POTASSIUM CHANNEL? OR K CHANNEL?
L7 5157 S L6 AND (TUMOR OR CANCER OR GLIOMA OR INFECTION OR STROKE OR
L8 4 S L3 AND L7
L9 3 DUP REM L8 (1 DUPLICATE REMOVED)
L10 1522 S L6 AND (TUMOR OR CANCER OR GLIOMA)
L11 1 S L3 AND L10

=> s drug deliver and l6
L12 0 DRUG DELIVER AND L6

=> s l10 and blood brain barrier
L13 1 L10 AND BLOOD BRAIN BARRIER

=> d bib abs

L13 ANSWER 1 OF 1 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 92283611 EMBASE
DN 1992283611
TI Endothelin increases rubidium uptake through calcium-activated ***potassium*** ***channels*** in C6 ***glioma*** cells.
AU Supattapone S.; Ashley C.C.
CS University Laboratory of Physiology,Oxford OX1 3PT, United Kingdom
SO Annals of the New York Academy of Sciences, (1991) 633/- (597-598). ISSN: 0077-8923 CODEN: ANYAA
CY United States
DT Journal; Conference Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry
037 Drug Literature Index
LA English

=> s l10 and brady?
L14 59 L10 AND BRADY?

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15 37 DUP REM L14 (22 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 37 ANSWERS - CONTINUE? Y/(N):y

L15 ANSWER 1 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2001:307857 BIOSIS
DN PREV200100307857
TI BK channels in human ***glioma*** cells.
AU Ransom, Christopher B.; Sontheimer, Harald (1)
CS (1) Dept. of Neurobiology, University of Alabama, 1719 6th Ave. S., CIRC 545, Birmingham, AL, 35294: hws@nrc.uab.edu USA

SO Journal of Neurophysiology (Bethesda), (February, 2001) Vol. 85, No. 2, pp. 790-803. print.
ISSN: 0022-3077.
DT Article
LA English
SL English
AB Ion channels in inexcitable cells are involved in proliferation and volume regulation. ***Glioma*** cells robustly proliferate and undergo shape and volume changes during invasive migration. We investigated ion channel expression in two human ***glioma*** cell lines (D54MG and STTG-1). With low (Ca2+)i, both cell types displayed voltage-dependent currents that activated at positive voltages (more than +50 mV). Current density was sensitive to intracellular cation replacement with the following rank order; K+ > Cs+ apprxeq Li+ > Na+. Currents were >80% inhibited by iberiotoxin (33 nM), charybdotoxin (50 nM), quinine (1 mM), tetrandrine (30 muM), and tetraethylammonium ion (TEA; 1 mM). Extracellular phloretin (100 muM), an activator of BK(Ca2+) channels, and elevated intracellular Ca2+ negatively shifted the I-V curve of whole cell currents. With 0, 0.1, and 1 muM (Ca2+)i, the half-maximal voltages, V0.5, for whole cell current activation were +150, +65, and +12 mV, respectively. Elevating (K+)o potentiated whole cell currents in a fashion proportional to the square-root of (K+)o. Recording from cell-attached patches revealed large conductance channels (150-200 pS) with similar voltage dependence and activation kinetics as whole cell currents. These data indicate that human ***glioma*** cells express large-conductance, Ca2+-activated K+ (BK) channels. In amphotericin-perforated patches ***bradykinin*** (1 muM) activated TEA-sensitive currents that were abolished by preincubation with bis-(o-aminophenoxy)-N,N,N',N'-tetraacetic acid-AM (BAPTA-AM). The BK channels described here may influence the responses of ***glioma*** cells to stimuli that increase (Ca2+)i.

L15 ANSWER 2 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:94144 BIOSIS
DN PREV200200094144
TI Signal transduction of ischemic preconditioning.
AU Schulz, Rainer; Cohen, Michael V.; Behrends, Matthias; Downey, James M.; Heusch, Gerd (1)
CS (1) Department of Pathophysiology, University of Essen, Hufelandstrasse 55, 45122, Essen: gerd.heusch@uni-essen.de Germany
SO Cardiovascular Research, (November, 2001) Vol. 52, No. 2, pp. 181-198. print.
ISSN: 0008-6363.
DT General Review
LA English

L15 ANSWER 3 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2000:476558 BIOSIS
DN PREV200000476558
TI Expression and function of endothelial Ca2+-activated ***K*** + ***channels*** in human mesenteric artery: A single-cell reverse transcriptase-polymerase chain reaction and electrophysiological study in situ.
AU Koehler, Ralf; Degenhardt, Christiane; Kuehn, Meike; Runkel, Norbert; Paul, Martin; Hoyer, Joachim (1)
CS (1) Benjamin Franklin Medical Center, Hindenburgdamm 30, 12200, Berlin Germany
SO Circulation Research, (September 15, 2000) Vol. 87, No. 6, pp. 496-503. print.
ISSN: 0009-7330.
DT Article
LA English
SL English
AB Ca2+-activated K+ (KCa) channels have been suggested to play a role in the control of endothelial functions such as regulation of vascular tone and cell proliferation. We established a method for single-cell reverse transcriptase-polymerase chain reaction analysis in combination with the patch-clamp technique to characterize KCa channel expression and function in single endothelial cells (ECs) within the endothelial monolayer of intact human mesenteric arteries (MAs) and in disease states. We tested whether endothelial KCa channel expression and function are altered in MAs obtained from patients with colonic adenocarcinoma (CA) compared with those in MAs from non- ***cancer*** patients with inactive diverticulitis. Expression of the intermediate-conductance KCa channel (hIK1) was detected in non- ***cancer*** and CA patients. In whole-cell patch-clamp measurements, only ECs expressing hIK1 exhibited corresponding KCa currents, whereas respective KCa currents were missing in hIK1-negative ECs. This heterogeneity of hIK1 expression patterns is indicative of a specialized subset of ECs within the endothelial monolayer. In CA patients, compared with non- ***cancer*** patients, a 2.5-fold increase in hIK1-expressing ECs per MA was observed (P<0.05). However, KCa current densities in hIK1-expressing ECs of both groups were similar. In addition to hIK1, expression of the large-conductance KCa channel (hSlo) was detected in single ECs from CA patients. The increased KCa channel expression in CA patients resulted in a 2.7-fold increase of ***bradykinin*** -induced endothelial hyperpolarization compared with controls (P<0.05). This increased expression and function of KCa channels might indicate an altered functional state of the endothelium in ***cancer*** patients and could play a role in ***tumor*** angiogenesis.

L15 ANSWER 4 OF 37 MEDLINE
AN 2000443750 MEDLINE
DN 20447458 PubMed ID: 10988242
TI Expression and function of endothelial Ca(2+)-activated ***K*** (+) ***channels*** in human mesenteric artery: A single-cell reverse transcriptase-polymerase chain reaction and electrophysiological study in situ.
AU Kohler R; Degenhardt C; Kuhn M; Runkel N; Paul M; Hoyer J
CS Department of Nephrology, Benjamin Franklin Medical Center, Freie Universitat, Berlin, Germany.
SO CIRCULATION RESEARCH, (2000 Sep 15) 87 (6) 496-503.
Journal code: DAJ; 0047103. ISSN: 1524-4571.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200010
ED Entered STN: 20001012
Last Updated on STN: 20010521
Entered Medline: 20001003
AB Ca(2+)-activated K(+) (K(Ca)) channels have been suggested to play a role in the control of endothelial functions such as regulation of vascular tone and cell proliferation. We established a method for single-cell reverse transcriptase-polymerase chain reaction analysis in combination with the patch-clamp technique to characterize K(Ca) channel expression and function in single endothelial cells (ECs) within the endothelial monolayer of intact human mesenteric arteries (MAs) and in disease states. We tested whether endothelial K(Ca) channel expression and function are altered in MAs obtained from patients with colonic adenocarcinoma (CA) compared with those in MAs from non- ***cancer*** patients with inactive diverticulitis. Expression of the intermediate-conductance K(Ca) channel (hIK1) was detected in non- ***cancer*** and CA patients. In whole-cell patch-clamp measurements, only ECs expressing hIK1 exhibited corresponding K(Ca) currents, whereas respective K(Ca) currents were missing in hIK1-negative ECs. This heterogeneity of hIK1 expression patterns is indicative of a specialized subset of ECs within the endothelial monolayer. In CA patients, compared with non- ***cancer*** patients, a 2.5-fold increase in hIK1-expressing ECs per MA was observed (P:<0.05). However, K(Ca) current densities in hIK1-expressing ECs of both groups were similar. In addition to hIK1, expression of the large-conductance K(Ca) channel (hSlo) was detected in single ECs from CA patients. The increased K(Ca) channel expression in CA patients resulted in a 2. 7-fold increase of ***bradykinin*** -induced endothelial hyperpolarization compared with controls (P:<0.05). This increased expression and function of K(Ca) channels might indicate an altered functional state of the endothelium in ***cancer*** patients and could play a role in ***tumor*** angiogenesis.

L15 ANSWER 5 OF 37 MEDLINE
AN 2001140898 MEDLINE
DN 21078486 PubMed ID: 11211107
TI Both linopirdine- and WAY123,398-sensitive components of I K(M,ng) are modulated by cyclic ADP ribose in NG108-15 cells.
AU Higashida H; Brown D A; Robbins J
CS Department of Biophysical Genetics, Kanazawa University Graduate School of Medicine, Japan.
SO PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (2000 Dec) 441 (2-3) 228-34.
Journal code: OZX; 0154720. ISSN: 0031-6768.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308
AB The "M-like" current in NG108-15 cells has two components carried by different ***K*** + ***channels*** : a fast-deactivating component, analogous to IK(M) in sympathetic neurones and carried by KCNQ2/3 channels, and a more slowly deactivating component carried by murine erg1 (merg1) channels. The former is selectively blocked by linopirdine (< or =10 microM), the latter by WAY123,398 (< or =10 microM). ***Bradykinin*** (100 nM) inhibited 76% of the KCNQ component of current compared with 12% of the merg component. Cyclic ADP ribose (cADPR, 2 microM), introduced via the patch pipette, caused a rundown of both current components. Acetylcholine (100 microM) inhibited 89% of the KCNQ component of current compared to 34% of the merg component. After 15 min of intracellular dialysis with the cADPR antagonist 8-amino-cADP ribose (100 microM), the inhibition reduced to 40% and 19% and after 30 min it was further reduced to 8% and 5% for the KCNQ currents and merg currents respectively. These data show that both KCNQ and merg currents in NG108-15 cells can be modulated by either ***bradykinin*** or M1 muscarinic receptors. The inhibition of the KCNQ current component is more pronounced than that of the merg component. These results suggest that cADPR might be involved in M1-muscarinic inhibition of both KCNQ2/3 and merg1 channels.

L15 ANSWER 6 OF 37 MEDLINE
AN 1999383610 MEDLINE
DN 99383610 PubMed ID: 10455268
TI Separation of M-like current and ERG current in NG108-15 cells.
AU Meves H; Schwarz J R; Wulfsen I

CS Physiologisches Institut, Universitat des Saarlandes, Homburg-Saar, Germany.
SO BRITISH JOURNAL OF PHARMACOLOGY, (1999 Jul) 127 (5) 1213-23. Journal code: B00; 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991005
AB Differentiated NG108-15 neuroblastoma x ***glioma*** hybrid cells were whole-cell voltage-clamped. Hyperpolarizing pulses, superimposed on a depolarized holding potential (-30 or -20 mV), elicited deactivation currents which consisted of two components, distinguishable by fitting with two exponential functions. Linopirdine [DuP 996, 3,3-bis(4-pyridinylmethyl)-1-phenylindolin-2-one), a neurotransmitter-release enhancer known as potent and selective blocker of the M-current of rat sympathetic neurons, in concentrations of 5 or 10 microM selectively inhibited the fast component (IC50 = 14.7 microM). The slow component was less sensitive to linopirdine (IC50>20 microM). The class III antiarrhythmics [(4-methylsulphonyl)amido]benzenesulphonamide (WAY-123.398) and 1-[2-(6-methyl-2-pyrydinil)ethyl]-4-(4-methylsulphonylaminobenz oyl) piperidine (E-4031), selective inhibitors of the inwardly rectifying ERG (ether-a-go-go-related gene) ***potassium*** ***channel*** , inhibited predominantly the slow component (IC50 = 38 nM for E-4031). The time constant of the WAY-123.398-sensitive current resembled the time constant of the slow component in size and voltage dependence. Inwardly rectifying ERG currents, recorded in K+ -rich bath at strongly negative pulse potentials, resembled the slow component of the deactivation current in their low sensitivity to linopirdine (28% inhibition at 50 microM). The size of the slow component varied greatly between cells. Accordingly, varied the effect of WAY-123.398 on deactivation current and holding current. RNA transcripts for the following members of the ether-a-go-go gene (EAG) ***K*** + ***channel*** family were found in differentiated NG108-15 cells: ERG1, ERG2, EAGl, EAG-like (ELK)1, ELK2; ERG3 was only present in non-differentiated cells. In addition, RNA transcripts for KCNQ2 and KCNQ3 were found in differentiated and non-differentiated cells. We conclude that the fast component of the deactivation current is M-like current and the slow component is deactivating ERG current. The molecular correlates are probably KCNQ2/KCNQ3 and ERG1/ERG2, respectively.

L15 ANSWER 7 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
AN 1999:468743 BIOSIS
DN PREV199900468743
TI Leukotriene D4 (LTD4) activates charybdotoxin-sensitive and -insensitive ***K*** + ***channels*** in Ehrlich ascites ***tumor*** cells.
AU Hoffmann, Else Kay (1)
CS (1) August Krogh Institute, Biochemical Department, University of Copenhagen, Universitetsparken 13, DK-2100, Copenhagen O Denmark
SO Pfluegers Archiv European Journal of Physiology, (Aug., 1999) Vol. 438, No. 3, pp. 263-268. ISSN: 0031-6768.
DT Article
LA English
SL English
AB The putative role for ATP, UTP, ***bradykinin*** and leukotriene D4 (LTD4) in the activation of the charybdotoxin-insensitive, volume-activated K+ leak pathway has been assessed in Ehrlich cells. ***K*** + ***channel*** activity is evaluated from bumetanide-insensitive 86Rb+ efflux using Rb+ as a tracer for K+. Addition of the Ca2+-mobilizing agonists ***bradykinin*** , ATP, UTP or LTD4 accelerates the regulatory volume decrease (RVD) response and activates a fast bumetanide-insensitive, charybdotoxin-sensitive efflux of K+. In addition LTD4 activates a charybdotoxin-insensitive K+ efflux, whereas ***bradykinin*** , ATP and UTP do not. The charybdotoxin-insensitive K+ efflux dominates after addition of LTD4 at concentrations too low to elicit an increase in (Ca2+)i but still high enough to be effective in accelerating the RVD response. The EC50 values for LTD4-induced K+ effluxes are estimated at 2 nM and 15 nM for the charybdotoxin-insensitive and charybdotoxin-sensitive components, respectively. The LTD4 (cysLT1) receptor antagonist L660,711(MK-571) blocks the activation of the charybdotoxin-sensitive but not the charybdotoxin-insensitive K+ efflux. Thus, LTD4 activates two different K+ leak pathways in Ehrlich cells, one pathway activated by an increase in (Ca2+)i and the other via an alternative signalling pathway. LTD4 is thus a potential candidate for an autocrine messenger activating the Ca2+-independent, charybdotoxin-insensitive ***K*** + ***channel*** during the RVD response in Ehrlich cells.

L15 ANSWER 8 OF 37 MEDLINE
AN 1999299500 MEDLINE
DN 99299500 PubMed ID: 10370087
TI ***Bradykinin*** -stimulated Cl- secretion in T84 cells. Role of Ca2+-activated hSK4-like ***K*** + ***channels*** .
AU Huber S M; Tschop J; Braun G S; Nagel W; Horster M F
CS Physiologisches Institut der Ludwig-Maximilians-Universitat, Pettenkoferstrasse 12, D-80336 Munich, Germany.
SO PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1999 Jun) 438 (1) 53-60. Journal code: OZX; 0154720. ISSN: 0031-6768.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990730
AB ***Bradykinin*** (BK)-stimulated colonic Cl- secretion was studied in T84 colonic adenocarcinoma cells by measuring BK (50 nM)-evoked changes in cytosolic free [Ca2+] ([Ca2+]i), membrane conductance and transepithelial ion transport. In T84 cells grown on impermeable supports, BK stimulated a transient increase in [Ca2+]i as assessed by fura-2 ratio imaging. In cell-attached, patch-clamp recordings, BK transiently activated low-conductance ***K*** ***channels*** . These channels were activated/inactivated reversibly in inside-out patches by switching [Ca2+]i in the bath between 30 nM and 100 nM. Excised channels recorded with 160 mM [K+] in bath and pipette exhibited an inwardly rectifying current/voltage-relation, conductances of 10+/-1 pS and 34+/-4 pS (n=10) at positive and negative voltages, respectively, and a 15-fold lower permeability for Na+ than for K+. The mean open probability of these channels did not depend on voltage but increased with increasing [Ca2+]i with an apparent concentration for a half-maximal response (EC50) of 110 nM, resembling that of hSK4 ***K*** + ***channels*** . Application of the reverse transcriptase-polymerase chain reaction technique showed hSK4 messenger ribonucleic acid (mRNA) to be expressed in T84 cells. Macroscopic currents in T84 cells showed a similar dependence on [Ca2+]i. Whole cell conductance (in nS/10pF) increased from 0.5+/-0. 1 (n=6) at 10 nM [Ca2+]i in the pipette solution to 1.5+/-0.2 (n=7) at 100 nM, and to 2.0+/-0.5 (n=7) at 1 microM due to activation of a K+ conductance. In Ussing-chambered T84 monolayers grown on filters, BK did not evoke a short-circuit current (Isc). When, however, the monolayers were pre-stimulated by forskolin (1 microM), BK further enhanced Cl-secretion (DeltaIsc=21+/-5 microA/cm2, n=10) transiently and biphasically. In conclusion, BK enhances cyclic adenosine monophosphate-stimulated Cl-secretion in T84 cells, probably via basolateral, Ca2+-liganded activation of low-conductance hSK4-type ***K*** + ***channels*** .

L15 ANSWER 9 OF 37 MEDLINE DUPLICATE 4
AN 97227112 MEDLINE
DN 97227112 PubMed ID: 9138690
TI The effects of ***bradykinin*** on K+ currents in NG108-15 cells treated with U73122, a phospholipase C inhibitor, or neomycin.
AU Hildebrandt J P; Plant T D; Meves H
CS Physiologisches Institut, Universitat des Saarlandes, Homburg-Saar, Germany.
SO BRITISH JOURNAL OF PHARMACOLOGY, (1997 Mar) 120 (5) 841-50. Journal code: B00; 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970502
AB 1. ***Bradykinin*** has multiple effects on differentiated NG108-15 neuroblastoma x ***glioma*** cells: it increases Ins(1,4,5)P3 production and intracellular Ca2+ concentration [Ca2+]i evokes a Ca2+ activated K+ current (IK(Ca)) and inhibits M current (IM). We studied the effect of the aminosteroid U73122 and the antibiotic neomycin, both putative blockers of phospholipase C (PLC), on these four ***bradykinin*** effects. 2. Preincubation with 1 or 5 microM U73122 for 15 min partly suppressed Ins(1,4,5)P3 generation and the increase in [Ca2+]i induced by 1 microM ***bradykinin*** . U73122 10 microM caused total and irreversible inhibition. The inactive analogue U73343 was without effect. 3. Resting levels of Ins(1,4,5)P3 were not affected. However, resting [Ca2+]i was increased by 10 microM U73122, but not by U73343. Individual cells responded to 10 microM U73122 with a small increase in [Ca2+]i, followed in some cells by a large further rise. 4. Pretreatment of whole-cell clamped cells with 1 microM U73122 for 30 min reduced the ***bradykinin*** -induced IK(Ca) to a fifth of its normal size. To suppress it totally, a 7-12 min pretreatment with 5 microM U73122 was required. Again, U73343 was without effect. 5. U73122 and U73343 at concentrations of 5-10 microM irreversibly decreased the holding current (Ih) which at a holding potential of -30 or -20 mV mainly flows through open M channels. The decrease was often preceded by a transient increase. 6. M current (IM) measured with 1 s pulses, was also decreased by 5-10 microM U73122 and U73343, but short applications of U73122 could cause a small increase. The ***bradykinin*** -induced inhibition of IM was not affected by U73122. 7. Preincubation with 1 or 3 mM neomycin for 15 min did not affect Ins(1,4,5)P3 generation and the increase in [Ca2+]i induced by ***bradykinin*** . Pretreatment with 3 mM neomycin for about 20 min diminished the ***bradykinin*** -induced IK(Ca) to a fifth of its normal size. 8. The four main conclusions drawn from the results are: (a) U73122 suppresses ***bradykinin*** -induced PLC activation and IK(Ca), but not IM inhibition. (b) This indicates that the transient outward current IK(Ca), but not the decrease of IM in response to ***bradykinin*** , is mediated by PLC. (c) U73122 itself inhibits IM and mobilizes Ca2+ from intracellular stores. (d) Externally applied neomycin

is not an effective inhibitor of PLC-mediated signalling pathways in NG108-15 cells.

L15 ANSWER 10 OF 37 MEDLINE
AN 96314301 MEDLINE
DN 96314301 PubMed ID: 8759103
TI Class III antiarrhythmic effects of zatebradine. Time-, state-, use-, and voltage-dependent block of hKv1.5 channels.
AU Valenzuela C; Delpon E; Franqueza L; Gay P; Perez O; Tamargo J; Snyders D
J
CS Institute of Pharmacology and Toxicology, CSIC, School of Medicine, Universidad Complutense, Madrid, Spain.
NC HL-47599 (NHLBI)
SO CIRCULATION, (1996 Aug 1) 94 (3) 562-70.
Journal code: DAW; 0147763. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961211
AB BACKGROUND: Zatebradine is a ***bradycardic*** agent that inhibits the hyperpolarization-activated current (I(f)) in the rabbit sinoatrial node. It also prolongs action potential duration in papillary muscles in guinea pigs and in Purkinje fibers in rabbits. The underlying mechanism by which zatebradine induces this effect has not been explored, but it is likely to involve ***K*** + ***channel*** block. METHODS AND RESULTS: Cloned human cardiac K+ delayed rectifer currents (hKv1.5) were recorded in Ltk- cells transfected with their coding sequence. Zatebradine 10 mumol/L did not modify the initial activation time course of the current but induced a subsequent decline to a lower steady-state current level with a time constant of 109 +/- 16 ms. Zatebradine inhibited hKv1.5 with an apparent KD of 1.86 +/- 0.14 mumol/L. Block was voltage dependent (electrical distance delta = 0.177 +/- 0.003) and accumulated in a use-dependent manner during 0.5- and 1-Hz pulse trains because of slower recovery kinetics in the presence of the drug. Zatebradine reduced the tail current amplitude, recorded at -30 mV, and slowed the deactivation time course, which resulted in a "crossover" phenomenon when control and zatebradine tail currents were superimposed. CONCLUSIONS: These results indicate that (1) zatebradine is an open-channel blocker of hKv 1.5, (2) binding occurs in the internal mouth of the ion pore, (3) unbinding is required before the channel can close, and (4) zatebradine-induced block is use dependent because of slower recovery kinetics in the presence of the drug. These effects may explain the prolongation of the cardiac action potential and could be clinically relevant.

L15 ANSWER 11 OF 37 MEDLINE
AN 96197805 MEDLINE
DN 96197805 PubMed ID: 8617371
TI M-type K+ current inhibition by a toxin fron the scorpion Buthus eupeus.
AU Filippov A K; Kozlov S A; Pluzhnikov K A; Grishin E V; Brown D A
CS Department of Pharmacology, University College London, UK.
SO FEBS LETTERS, (1996 Apr 22) 384 (3) 277-80.
Journal code: EUH; 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199606
ED Entered STN: 19960620
Last Updated on STN: 19970203
Entered Medline: 19960613
AB A number of invertebrate venoms have been tested for effects on M-type K+ currents (IK(M)) in differentiated mouse neuroblastoma X rat ***glioma*** NG108-15 cells. Among the venoms tested, Buthus eupeus scorpion venom reversibly inhibited IK(M) by approximately 44% at 50 microgram/ml. Inhibition was not due to activation of ***bradykinin*** or nucleotide (pyrimidine) receptors. On venom fractionation, a polypeptide of 4 kDa was purified that inhibited IK(M) by approximately 45% with an IC50 of approximately 33 nM. Neither the crude venom nor the purified polypeptide affected the Ca2+ current or the delayed rectifier K+ current. While the crude venom prolonged the Na+ current, the polypeptide did not. Thus, the 4 kDa Buthus eupeus polypeptide appears to be a selective inhibitor of IK(M) in NG108-15 cells.

L15 ANSWER 12 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:62386 BIOSIS
DN PREV199799361589
TI Modification of cellular ion transport by the Ha-ras oncogene: Steps towards malignant transformation.
AU Ritter, M. (1); Woell, E.
CS (1) Hosp. Intern. Med., Univ. Innsbruck, Anichstrasse 35, A-6010 Innsbruck Austria
SO Cellular Physiology and Biochemistry, (1996) Vol. 6, No. 5, pp. 245-270.
ISSN: 1015-8987.
DT General Review
LA English
AB Expression of the transforming Ha-ras oncogene in NIH 3T3 fibroblasts (+ras cells) results in growth-factor-independent proliferation, breakdown of actin stress fiber network and increase in intracellular pH and cell volume due to activation of the Na+/H+ exchanger and Na+, K+, 2Cl- cotransport. +ras cells respond to mitogens like serum or ***bradykinin*** with sustained oscillations of the cell membrane potential due tn stimulated calcium entry which triggers pulsatile release of calcium from internal stores and subsequent activation of calcium-sensitive ***K*** + ***channels*** . Calcium antagonists like bepridil or nifedipine inhibit cellular calcium entry and oscillations of the intracellular calcium concentration, protect +ras cells against actin stress fiber depolymerization, block activation of the Na+/H+ exchanger and inhibit cell proliferation. Inhibition of the Na+/H+ exchanger inhibits the increase in the intracellular pH and cell proliferation but does not alter cytoskeletal rearrangement, calcium entry or oscillations of intracellular calcium. In cells not expressing the oncogene (-ras cells), ***bradykinin*** causes a single transient hyperpolarization, is without effect on cytoarchitecture and leads to cell shrinkage unless actin filament disruption is induced by cytochalasin D or pretreatment of the cells with LiCl. Apparently the oscillations of intracellular calcium are required for depolymerization of the actin filaments and for activation of the Na+/H+ exchanger. Thus the alterations of ion transport are prerequisites for growth-factor-independent proliferation of Ha-ras-oncogene-expressing cells.

L15 ANSWER 13 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 1996:216637 BIOSIS
DN PREV199698772766
TI (Ca-2+)-i oscillations induced by ***bradykinin*** in rat ***glioma*** cells associated with Ca-2+ store-dependent Ca-2+ influx are controlled by cell volume and by membrane potential.
AU Reetz, Guido; Reiser, Georg (1)
CS (1) Inst. Neurobiochem., Med. Fak., Otto-von-Guericke-Univ. Magdeburg, Leipziger Str. 44, 39120 Magdeburg Germany
SO Cell Calcium, (1996) Vol. 19, No. 2, pp. 143-156.
ISSN: 0143-4160.
DT Article
LA English
AB Long-term superfusion with ***bradykinin*** causes oscillations of cytosolic Ca-2+ activity ((Ca-2+)-i) in Fura-2 loaded rat ***glioma*** cells. The (Ca-2+)-i rise is associated with synchronous plasma membrane hyperpolarization oscillating with a frequency of 0.8-1.8 per min. The initial large transient (Ca-2+)-i rise, induced immediately with ***bradykinin*** admission results from InsP-3-mediated Ca-2+ release, whereas the subsequent oscillations depend mainly on Ca-2+ influx, as demonstrated: (i) by blockade of (Ca-2+)-i oscillations by reduction of (Ca-2+)-ex, or addition of Ca-2+-channel blockers; and (ii) evidence from Mn-2+ quench experiments. Suppression of (Ca-2+)-i oscillations with high K+ depolarization and with block of Ca-2+-dependent ***K*** + ***channels*** proves that membrane hyperpolarization is required for Ca-2+ influx during the oscillation. Ca-2+ release from intracellular stores by inhibitors of endoplasmic reticulum Ca-2+-ATPase attenuates or blocks the (Ca-2+)-i oscillations. This suggests that ***bradykinin*** -induced Ca-2+ influx is controlled by the filling state of the stores. The (Ca-2+)-i oscillations are suppressed by hypertonic medium and enhanced by hypotonic medium. Cell swelling enhances Ca-2+ influx. We propose the following model for generation of the oscillations in the glial cell line: InsP-3-induced Ca-2+ release from internal stores periodically evokes Ca-2+ influx through Ca-2+-permeable cation channels. Hyperpolarization of the plasma membrane due to the activation of Ca-2+-dependent ***K*** + ***channels*** enhances the Ca-2+ influx. The concomitant K+ efflux could lead to cell shrinkage which suppresses Ca-2+ influx. Cell volume and membrane potential probably serve as feedback regulators during the (Ca-2+)-i oscillations.

L15 ANSWER 14 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 95185561 EMBASE
DN 1995185561
TI The effect of barium on [3H]noradrenalin release from the human neuroblastoma SH-SY5Y.
AU Vaughan P.F.T.; Kaye D.F.; Ball S.G.; Reeve H.L.; Peers C.
CS Department of Vascular Studies, University of Leeds,Leeds LS2 9TJ, United Kingdom
SO European Journal of Neuroscience, (1995) 7/5 (875-880).
ISSN: 0953-816X CODEN: EJONEI
CY United Kingdom
DT Journal; Article
FS 002 Physiology
008 Neurology and Neurosurgery
029 Clinical Biochemistry
LA English
SL English
AB Replacement of Ca2+ with Ba2+ in HEPES-buffered saline stimulated [3H]noradrenalin release in the human neuroblastoma clone SH-SY5Y by up to 20% of the cell content in the absence of other secretory stimuli. The Ba2+-evoked release was inhibited by 85% by 3 .mu.M tetrodotoxin and 95% by 5 .mu.M nifedipine. Ba(2+) also increased the potency of K+-evoked release of [3H]noradrenalin, as maximal release was observed with 60 mM K+ compared with the 100 mM K+ necessary to achieve maximal release in the presence of Ca2+. In contrast, replacing Ca2+ with Ba(2+) had little effect on carbachol- and ***bradykinin*** -evoked release of [3H]noradrenalin. No evidence was obtained from studies on changes in [Ca2+](i) (in response to 100 .mu.M carbachol) using fura-2 that Ba2+

could enter intracellular stores in SH-SY5Y cells. Whole-cell patch-clamp studies showed that Ba2+ depolarizes SH-SY5Y cells as well as enhancing inward Ca2+ channel currents and shifting their voltage dependence to more negative values. These results are discussed in terms of the hypothesis that Ba2+ blocks ***K*** + ***channels*** , leading to depolarization followed by opening of voltage-sensitive Na+ channels. This in turn opens voltage-sensitive L-type Ca2+ channels, which are coupled to the release of [3H]noradrenalin in SH-SY5Y cells.

L15 ANSWER 15 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
AN 1996:125684 BIOSIS
DN PREV199698697819
TI Regulation of insulinoma cell proliferation and insulin accumulation by peptides and second messengers.
AU Sjoholm, Ake
CS Dep. Mol. Med., Endocrine Diabetes Unit, Rolf Luft Cent. Diabetes Res., Karolinska Inst., Karolinska Hosp., S-171 76 Stockholm Sweden
SO Upsala Journal of Medical Sciences, (1995) Vol. 100, No. 3, pp. 201-216. ISSN: 0300-9734.
DT Article
LA English
AB The regulation of clonal rat insulinoma (RINm5F) cell proliferation and hormone accumulation was investigated with the aim of identifying putative compounds capable of inducing differentiation, i.e. decreased growth and increased insulin accumulation, by the ***tumor*** cells. In particular, interest was focused on the role of a number of peptides as well as pharmacological probes modulating various signal transduction systems and which have been shown to regulate normal beta-cell proliferation and insulin accumulation. Growth hormone stimulated insulin accumulation and inhibited DNA synthesis, whereas galanin and insulin-like growth factor I caused a moderate suppression of insulin accumulation but did not affect proliferation, while epidermal growth factor, transforming growth factor beta, platelet-derived growth factor, acidic and basic fibroblast growth factor, ***bradykinin*** and somatostatin were virtually inactive on all parameters tested. Exogenous prostaglandins E-2 and F-1alpha were inactive, while the cyclooxygenase inhibitor indomethacin slightly suppressed insulin accumulation. The cytokine IL-1-beta caused a significant decrease in both beta-cell mitogenesis and insulin accumulation, effects that were mediated through nitric oxide generation. The vitamin A derivative retinyl acetate slightly inhibited serum-stimulated DNA synthesis, but did not affect insulin accumulation. The vitamin E alpha-tocopherol significantly enhanced insulin release but did not affect mitogenesis. By contrast, gamma-tocopherol was inactive on both these parameters. The alpha-adrenergic agonist clonidine evoked a slight inhibition of serum-stimulated DNA synthesis, without influencing insulin accumulation, whereas phenylephrine did not affect any of these parameters. Carbamylcholine increased insulin accumulation, but not cell proliferation, whereas the adenylyl cyclase activator forskolin suppressed mitogenesis but did not affect insulin accumulation. Inhibition of protein kinase C with staurosporine or prolonged treatment with phorbol ester suppressed DNA synthesis, as did the tyrosine kinase inhibitor genistein. Stimulating Ca-2+ influx by closing ATP-dependent ***K*** + ***channels*** with glibenclamide enhanced DNA synthesis, while opening of these channels with diazoxide suppressed cell growth. Conversely, preventing Ca-2+ influx by the Ca-2+ channel antagonist D-600, chelating intracellular Ca-2+ by fura-2 AM or inhibiting the Ca-2+/calmodulin-dependent protein kinase by calmidazol resulted in a decreased DNA synthesis. On the other hand, uncontrolled influx or mobilization of Ca-2+ by ionomycin or thapsigargin resulted in an arrested DNA synthesis. The present paper shows that RINm5F insulinoma cell proliferation and insulin accumulation can be modulated by various peptidergic and pharmacological agents regulating certain signal transduction pathways. However, mitogenesis in the insulinoma cells seemingly is controlled in a vastly different manner in comparison to that in normal beta-cells. The most spectacular in this screening study, i.e. that growth hormone, contrarily to its effect on normal beta-cells, suppresses insulinoma cell growth, merits further elucidation of the underlying mechanisms. Possibly the hormone might become of utility in a clinical setting in the treatment of patients with insulin-producing tumors.

L15 ANSWER 16 OF 37 MEDLINE DUPLICATE 7
AN 96117782 MEDLINE
DN 96117782 PubMed ID: 8581401
TI Putative M-type ***potassium*** ***channels*** in neuroblastoma-***glioma*** hybrid cells: inhibition by muscarine and ***bradykinin*** .
AU Selyanko A A; Robbins J; Brown D A
CS Department of Pharmacology, University College London, UK.
SO RECEPTORS AND CHANNELS, (1995) 3 (2) 147-59. Journal code: B3Y; 9315376. ISSN: 1060-6823.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199603
ED Entered STN: 19960327
Last Updated on STN: 19970203
Entered Medline: 19960319
AB Putative M-type ***K*** (+)- ***channels*** ('M-channels') were recorded in differentiated NG108-15 neuroblastoma x ***glioma*** hybrid cells transformed to express m1 muscarinic acetylcholine receptors using cell-attached patch-electrodes. Channels showed multiple conductances, with peaks at 6-9 and 12-15 pS. Averaged currents showed time-dependent activation during 1 s depolarization steps to around -30 mV. Steady-state Po increased in a voltage-dependent manner when the membrane was depolarized between 10 and 60 mV, with a limiting slope of 5.5 mV/e-fold change in Po. Steady-state kinetics were fit by two open and three shut times: depolarization shortened shut times and lengthened open times. Application of muscarine (10 microM) or ***bradykinin*** (10 microM) to the membrane outside the patch reversibly reduced steady-state in-patch channel activity to 38.4 +/- 11.7 and 28.8 +/- 6.1% of control values, respectively. Inhibition was accompanied by a lengthening of channel shut times without significant change in open times or distribution of conductance levels. No effect of muscarine or ***bradykinin*** on whole-cell or membrane patch delayed rectifier currents was detected. It is concluded that M-channels in NG108-15 cells are qualitatively similar to, but sparser than, those previously reported in rat sympathetic neurones. Their inhibition by extra-patch acetylcholine and ***bradykinin*** suggests that a mobile messenger is involved in the transduction process leading from receptor activation to channel closure.

L15 ANSWER 17 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:440548 BIOSIS
DN PREV199598454848
TI Activation of Ca-2+ influx by transforming Ha-ras.
AU Maly, K.; Kindler, E.; Tinhofer, I.; Grunicke, H. H. (1)
CS (1) Inst. Med. Chem. Biochemistry, Univ. Innsbruck, Fritz-Preglstrasse 3, A-6020 Innsbruck Austria
SO Cell Calcium, (1995) Vol. 18, No. 2, pp. 120-134. ISSN: 0143-4160.
DT Article
LA English
AB The effect of an induction of transforming Ha-ras on Ca-2+ influx into NIH3T3 cells was studied employing Fura-2 quenching by Mn-2+. The expression of transforming p21-Ha-ras caused a significant increase in Mn-2+ influx which was blocked by Cd-2+, La-3+, niguldipine and the Ca-2+-channel blocker SK&F96365. This effect was specific for transforming Ha-ras and was not seen after overexpression of the Ha-ras proto-oncogene or v-mos. In addition to the enhanced Mn-2+ influx, transforming p21-Ha-ras elicited an increased efflux of the K+-congener 86Rb+ which was inhibitable by Ca-2+-channel blockers and charybdotoxin, a selective inhibitor of high and intermediate conductance Ca-2+-dependent ***K*** + ***channels*** . Charybdotoxin did not reduce the increase in Mn-2+ influx by ras, demonstrating that the activation of Ca-2+-dependent ***K*** + ***channels*** was not required for the sustained Mn-2+/Ca-2+ influx in the presence of transforming Ha-ras. In ras-expressing cells, the ***bradykinin*** -induced Mn-2+ influx and charybdotoxin sensitive 86Rb+ efflux were markedly potentiated. The increase in the inositol-1,4,5-trisphosphate and inositol-1,3,4,5-tetrakisphosphate levels by ras is not sufficient to explain the elevated Mn-2+ influx. The mitogenic response to an expression of transforming Ha-ras was inhibited by the Ca-2+-channel blockers not, however, by charybdotoxin. These data suggest the existence of an agonist-independent activation of a receptor- or second messenger-operated Ca-2+ channel by transforming Ha-ras which is necessary for the mitogenic response to the activation of the oncogene.

L15 ANSWER 18 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94153367 EMBASE
DN 1994153367
TI Calcium signaling induced by ***bradykinin*** is synergistically enhanced by high K+ in NG108-15 cells.
AU Chueh S.-H.; Kao L.-S.
CS Dept. of Biochemistry, National Defense Medical Center,Taipei, Taiwan,Province of China
SO American Journal of Physiology - Cell Physiology, (1994) 266/4 35-4 (C1006-C1012). ISSN: 0002-9513 CODEN: AJPCDD
CY United States
DT Journal; Article
FS 002 Physiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We report a novel phenomenon in which the cytosolic Ca2+ concentration ([Ca2+](i)) rise induced in neuroblastoma x ***glioma*** hybrid NG108-15 cells by ***bradykinin*** is synergistically enhanced by elevated extracellular K+ concentrations. Presence of extracellular Ca2+ during high-K+ treatment, but not after high-K+ treatment, was required for the synergism. In addition, when thapsigargin was added concurrently with high K+, ***bradykinin*** still induced a significantly higher [Ca2+](i) rise than in cells treated with thapsigargin only. Both ***bradykinin*** -induced inositol 1,4,5-trisphosphate (IP3) generation and the size of the internal Ca2+ pool were increased by high-K+ treatment. Our data suggest that changes in membrane potential itself induced by high K+ probably do not cause the synergistic effect. The synergistic effect is apparently due to the stimulatory effects of high K+ on [Ca2+](i), which in turn modulates IP3 generation and increases the size of intracellular Ca2+ pools. If ***bradykinin*** is added following high K+, the synergism can be accounted for by increases both in

IP3 production and in the size of the internal Ca2+ pools. If ***bradykinin*** is added simultaneously with high K+, enhanced Ca2+ release triggered by enhanced IP3 production is the major cause of the synergistic effects.

L15 ANSWER 19 OF 37 MEDLINE
AN 94121903 MEDLINE
DN 94121903 PubMed ID: 8292355
TI ***Bradykinin*** modulates potassium and calcium currents in neuroblastoma hybrid cells via different pertussis toxin-insensitive pathways.
AU Wilk-Blaszczak M A; Gutowski S; Sternweis P C; Belardetti F
CS Department of Pharmacology, University of Texas Southwestern Medical Center at Dallas 75235.
NC GM31954 (NIGMS)
GM47721 (NIGMS)
NS25186 (NINDS)
SO NEURON, (1994 Jan) 12 (1) 109-16.
Journal code: AN8; 8809320. ISSN: 0896-6273.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940314
Last Updated on STN: 20000303
Entered Medline: 19940301
AB In NG108-15 cells, ***bradykinin*** (BK) activates a potassium current (IK,BK) and inhibits the voltage-dependent calcium current (ICa,V). BK also stimulates a phosphatidylinositol-specific phospholipase C (PI-PLC). The subsequent release of inositol 1,4,5-trisphosphate and increase in intracellular calcium contribute to IK,BK, through activation of a calcium-dependent potassium current. In membranes from these cells, stimulation of PI-PLC by BK is mediated by Gq and/or G11, two homologous, pertussis toxin-insensitive G proteins. Here, we have investigated the role of Gq/11 in the electrical responses to BK. GTP gamma S mimicked and occluded both actions of BK, and both effects were insensitive to pertussis toxin. Perfusion of an anti-Gq/11 alpha antibody into the pipette suppressed IK,BK, but not the inhibition of ICa,V by BK. Thus, BK couples to IK,BK via Gq/11, but coupling to ICa,V is most likely via a different, pertussis toxin-insensitive G protein.

L15 ANSWER 20 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1994:214417 BIOSIS
DN PREV199497227417
TI Ca-2+-Dependent ***K*** + ***channel*** activity in rat ***glioma*** cells induced by ***Bradykinin*** stimulation and by inositol 1,4,5-trisphosphate injection.
AU Binmoeller, Franz-Josef; Reiser, Georg (1)
CS (1) Physiol.-chem. Inst., Univ. Tuebingen, Hoppe-Seyler-Str. 4, 72076 Tuebingen Germany
SO Cellular and Molecular Neurobiology, (1993) Vol. 13, No. 6, pp. 615-624. ISSN: 0272-4340.
DT Article
LA English
AB 1. A glial cell line derived from C6 rat ***glioma*** cells has been shown previously to respond to extracellular pulses of ***bradykinin*** or intracellular injection of inositol 1.4.5-trisphosphate (Ins-P-3) with a slow hyperpolarizing response due to activation of a K+ current (G. Reiser et al, Brain Res. 506, 205-214; 1990). 2. We determined the ensuing single-channel activity, which is most likely caused by Ca-2+ released from internal stores after ***bradykinin*** stimulation. ***Bradykinin*** -activated channels were selectively permeable to K+, but not to Na+ or to Cl-, and exhibited conductances of mainly 40 and 50 pS. In ***glioma*** cells the same type of channel was activated by intracellular injection of Ins-P-3 and by extracellular ***bradykinin*** pulses.

L15 ANSWER 21 OF 37 MEDLINE
AN 93173580 MEDLINE
DN 93173580 PubMed ID: 8437887
TI Agonist-induced inhibition of inositol-trisphosphate-activated IK(Ca) in NG108-15 neuroblastoma hybrid cells.
AU Robbins J
CS Department of Pharmacology, University College London, UK.
SO PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1993 Jan) 422 (4)
364-70.
Journal code: OZX; 0154720. ISSN: 0031-6768.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930402
Last Updated on STN: 19970203
Entered Medline: 19930322
AB IK(Ca) activated by intracellular ionophoresis of inositol trisphosphate (IP3) or pressure-applied acetylcholine was inhibited by ***bradykinin*** and acetylcholine in NG108-15 cells transfected with m1 receptors. The inhibition of the IP3-evoked current was complete at 10 microM acetylcholine. This inhibition was not seen if the current was evoked by intracellular ionophoresis of calcium ions. Only receptors the activate the phosphoinositide system in these cells produced this inhibition, i.e. transfected muscarinic m1 and m3 and ***bradykinin*** receptors, but not muscarinic m2, m4 or adrenergic alpha 2 receptors. This inhibition was not sensitive to pertussis toxin or staurosporine. The concentrations of acetylcholine needed to inhibit the evoked current were identical to those needed to raise intracellular calcium but tenfold less than those needed for the agonist to activate IK(Ca). In a normal calcium-containing superfusate, recovery from inhibition required around 8 min (half-time 4 min) after removal of acetylcholine. When the experiment was performed in calcium-free medium no recovery was seen after 8 min washing in drug-free solution, but complete recovery was seen within 3 min (half-time 1.5 min) after adding calcium. Responses to repeated pressure applications of acetylcholine could be reversibly inhibited by acetylcholine and ***bradykinin*** . It seems, then, that there is no direct action of acetylcholine or ***bradykinin*** on the IK(Ca) channels themselves but that concentrations below those needed to activate IK(Ca) can empty and inhibit the IP3-sensitive calcium store. This may provide a mechanism for heterologous desensitization for phospholipase-C-linked receptor-mediated responses.

L15 ANSWER 22 OF 37 MEDLINE
AN 94096302 MEDLINE
DN 94096302 PubMed ID: 8271196
TI On the mechanism of M-current inhibition by muscarinic m1 receptors in DNA-transfected rodent neuroblastoma x ***glioma*** cells.
AU Robbins J; Marsh S J; Brown D A
CS Department of Pharmacology, University College London.
SO JOURNAL OF PHYSIOLOGY, (1993 Sep) 469 153-78.
Journal code: JQV; 0266262. ISSN: 0022-3751.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199401
ED Entered STN: 19940215
Last Updated on STN: 20000303
Entered Medline: 19940131
AB 1. Acetylcholine (ACh) produces two membrane current changes when applied to NG108-15 mouse neuroblastoma x rat ***glioma*** hybrid cells transformed (by DNA transfection) to express m1 muscarinic receptors: it activates a Ca(2+)-dependent K+ conductance, producing an outward current, and it inhibits a voltage-dependent K+ conductance (the M conductance), thus diminishing the M-type voltage-dependent K+ current (IK(M)) and producing an inward current. The present experiments were undertaken to find out how far inhibition of IK(M) might be secondary to stimulation of phospholipase C, by recording membrane currents and intracellular Ca2+ changes with indo-1 using whole-cell patch-clamp methods. 2. Bath application of 100 microM ACh reversibly inhibited IK(M) by 47.3 +/- 3.2% (n = 23). Following pressure-application of 1 mM ACh, the mean latency to inhibition was 420 ms at 35 degrees C and 1.79 s at 23 degrees C. Latencies to inhibition by Ba2+ ions were 148 ms at 35 degrees C and 92 ms at 23 degrees C. 3. The involvement of a G-protein was tested by adding 0.5 mM GTP-gamma-S or 10 mM potassium fluoride to the pipette solution. These slowly reduced IK(M), with half-times of about 30 and 20 min respectively, and rendered the effect of superimposed ACh irreversible. Effects of ACh were not significantly changed after pretreatment for 24 h with 500 ng ml-1 pertussis toxin or on adding up to 10 mM GDP-beta-S to the pipette solution. 4. The role of phospholipase C and its products was tested using neomycin (to inhibit phospholipase C), inositol 1,4,5-trisphosphate (InsP3) and inositol 1,3,4,5-tetrakisphosphate (InsP4), heparin, and phorbol dibutyrate (PDBu) and staurosporin (to activate and inhibit protein kinase C respectively). Both neomycin (1 mM external) and InsP3 (100 microM intrapipette) inhibited the ACh-induced outward current and/or intracellular Ca2+ transient but did not block ACh-induced inhibition of IK(M). Intrapipette heparin (1 mM) blocked activation of IK(Ca) and reduced Ach-induced inhibitions of IK(M), but also reduced inhibition of ICa via endogeneous m4 receptors. PDBu (with or without intrapipette ATP) and staurosporin had no significant effects.(ABSTRACT TRUNCATED AT 400 WORDS)

L15 ANSWER 23 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1993:380494 BIOSIS
DN PREV199345051919
TI ***Bradykinin*** -evoked inositol phosphate/calcium-dependent responses and ***potassium*** ***channels*** in neuroblastoma x ***glioma*** hybrid NG108-15 cells.
AU Higashida, Haruhiro
CS Dep. Biophysics, Neuroinfomation Res. Inst., Kanazawa Univ. Sch. Med., Kanazawa 920 Japan
SO Japanese Journal of Pharmacology, (1993) Vol. 61, No. SUPPL. 1, pp. 46P. Meeting Info.: 66th Annual Meeting of the Japanese Pharmacological Society Yokohama, Japan March 24-27, 1993
ISSN: 0021-5198.
DT Conference
LA English

L15 ANSWER 24 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94030749 EMBASE
DN 1994030749
TI K(M)-channels in rodent neuroblastoma x ***glioma*** hybrid cells

transfected with muscarinic m1 receptors: Inhibition by muscarine and ***bradykinin*** .
AU Robbins J.; Selyanko A.A.; Brown D.A.
CS Department of Pharmacology, University College London,London WC1E 6BT, United Kingdom
SO Journal of Physiology, (1993) 473/- (46P).
ISSN: 0022-3751 CODEN: JPHYA7
CY United Kingdom
DT Journal; Conference Article
FS 002 Physiology
LA English

L15 ANSWER 25 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9
AN 1992:413115 BIOSIS
DN BA94:76315
TI KINETIC AND PHARMACOLOGICAL PROPERTIES OF THE M-CURRENT IN RODENT NEUROBLASTOMA X ***GLIOMA*** HYBRID CELLS.
AU ROBBINS J; TROUSLARD J; MARSH S J; BROWN D A
CS DEP. PHARMACOL., UNIV. COLL. LONDON, GOWER STREET, LONDON WC1E 6BT.
SO J PHYSIOL (CAMB), (1992) 451 (0), 159-185.
CODEN: JPHYA7. ISSN: 0022-3751.
FS BA; OLD
LA English
AB 1. The M-like current IK(M,ng) in differentiated NG108-15 mouse neuroblastoma .times. rat ***glioma*** hybrid cells has been studied using tight-seal, whole-cell patch clamp recording. 2. When calculated from steady-state current-voltage curves, the conductance underlying IK(M,ng) showed a Boltzmann dependence on voltage with half-activation voltage Vo = -44 mV (in 3 mM [K+]) and slope factor (.alpha.) = 8.1 mV/e-fold increase in conductance. In 12 mM [K+] Vo = -38 mV and .alpha. =6.9 mV. The deactivation reciprocal time constant accelerated with hyperpolarization with slope factor 17 mV/e-fold voltage change. 3. The reversal potential for deactivation tail currents varied with external [K+] as if PNa/PK were 0.005. 4. Steady-state current was increased on removing external Ca2+. In the presence of external Ca2+, reactivation of IK(M,ng) after a hyperpolarizing step was delayed. This delay was preceded by an inward Ca2+ current, and coincided with an increase in intracellular [Ca2+] as measured with Indo-1 fluorescence. Elevation of intracellular [Ca2+] with caffeine also reduced IK(M,ng). 5. IK(M,ng) was inhibited by external divalent cations in decreasing order of potency (mM IC50 in parentheses): Zn2+ (0.011) > Cu2+ (0.018) > Cd2+ (0.070) > Ni2+ (0.44) > Ba2+ (0.47) > Fe2+ (0.69) > Mn2+ (0.86) > Co2+ (0.92) > Ca2+ (5.6) > Mg2+ (16) > Sr2+ (33). This was not secondary to inhibition of Ica since: (i) inhibition persisted in Ca2+-free solution; (ii) La3+ did not inhibit IK(M,ng) at concentrations which inhibited Ica; and (iii) organic Ca2+ channel blockers were ineffective. Inhibition comprised both depression of the maximum conductance and a positive shift of the activation curve. Addition of Ca2+ (10 .mu.M free [Ca2+]) or Ba2+ (1 mM total [Ba2+]) to the pipette solutions did not significantly change IK(M,ng). 6. IK(M,ng) was reduced by 9-amino-1,2,3,4-tetrahydroacridine (IC50 8 .mu.M) and quinine (30 .mu.M) but was insensitive to tetraethylammonium (IC50 > 30 mM), 4-aminopyridine (> 10 nM), apamin (> 3 .mu.M) or dendrotoxin (> 100 nM). 7. IK(M,ng) was inhibited by ***bradykinin*** (1-10 .mu.M) or angiotensin II (1-10 .mu.M), but not by the following other receptor agonists: acetylcholine (10 mM), muscarine (10 .mu.M), noradrenaline (100 .mu.M), adrenaline (100 .mu.M), dopamine (100 .mu.M), histamine (100 .mu.M), 5-hydroxytryptamine (10 .mu.M), Met-enkephaline (1 .mu.M), glycine (100 .mu.M), .gamma.-aminobutyric acid (100 .mu.M) or baclofen (500 .mu.M). 8. Inhibition of IK(M,ng) with Ba2+ did not change the zero-current potential but suppressed outward rectification of the current-voltage curve and facilitated repetitive action potential discharges produced by depolarizing current injections. This latter action potential discharges produced by depolarizing current injections. This latter action was not imitated by tetraethylammonium, apamin or 4-aminopyridine. 9. It is concluded that IK(M,ng) resembles the M-current recorded in sympathetic ganglia in (i) kinetic behaviour, (ii) inhibition by transient rises in intracellular [Ca2+], and (iii) functional effects. It differs from the ganglionic M-current in certain pharmacological properties (sensitivity to divalent cations, organic ***K*** + ***channel*** blockers and receptor agonists).

L15 ANSWER 26 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 92080148 EMBASE
DN 1992080148
TI Effect of calcium channel antagonists on cell membrane potential oscillations and proliferation of cells expressing the ras oncogene.
AU Woll E.; Weiss H.; Waldegger S.; Lang F.
CS Institute for Physiology, University of Innsbruck, Fritz-Pregl-Strasse 3, A-6010 Innsbruck, Austria
SO European Journal of Pharmacology, (1992) 212/1 (105-107).
ISSN: 0014-2999 CODEN: EJPHAZ
CY Netherlands
DT Journal; Article
FS 002 Physiology
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB NIH fibroblasts expressing the Ha-ras oncogene (+ras), unlike otherwise identical cells not expressing the oncogene (-ras), are able to grow in serum-depleted media (0.5% fetal calf serum). Electrophysiological experiments revealed that in +ras fibroblasts but not in -ras fibroblasts, ***bradykinin*** leads to sustained, calcium-dependent oscillations of cell membrane potential by repetitive activation of calcium-sensitive ***K*** + ***channels*** , resulting from oscillating intracellular calcium activity. The present study was performed to test for an effect of calcium channel antagonists on these phenomena. Whereas 10 .mu.mol/l verapamil and 10 .mu.mol/l diltiazem did not significantly interfere with either oscillations or proliferation, 10 .mu.mol/l nifedipine completely abolished both the oscillations and the proliferation of +ras fibroblasts. The number of -ras fibroblasts remained virtually constant in both the presence and absence of 10 .mu.mol/l nifedipine. These observations show the antiproliferative action of nifedipine and suggest that the oscillations of cell membrane potential are pertinent for the proliferation of +ras cells in serum-depleted media.

L15 ANSWER 27 OF 37 MEDLINE DUPLICATE 10
AN 93098015 MEDLINE
DN 93098015 PubMed ID: 1281376
TI Effects of ***bradykinin*** on ion conductances in NG108-15 neuroblastoma x ***glioma*** hybrid cells recorded with patch-clamp electrodes.
AU Robbins J; McFadzean I; Brown D A
CS Department of Pharmacology, University College London, U.K.
SO AGENTS AND ACTIONS. SUPPLEMENTS, (1992) 38 (Pt 2) 98-107.
Journal code: 2YH; 7801014. ISSN: 0379-0363.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199301
ED Entered STN: 19930129
Last Updated on STN: 19960129
Entered Medline: 19930113
AB Under whole-cell recording, ***bradykinin*** (BK) produced an initial outward membrane current followed by an inward current in voltage-clamped NG108-15 cells. The initial outward current was associated with a rise in intracellular Ca2+ and was accompanied by the opening of Ca(2+)-dependent ***K*** (+)- ***channels*** recorded with a cell-attached patch electrode. This current was inhibited by intracellular Mg2+. The inward current was associated with inhibition of the voltage-dependent K(+)-current IK(M). These effects accord with those previously observed in microelectrode-impaled cells, with the difference that BK produced much more pronounced and long-lasting desensitization in the patch-clamped cells.

L15 ANSWER 28 OF 37 MEDLINE
AN 91223851 MEDLINE
DN 91223851 PubMed ID: 1673906
TI Phosphoinositides and synaptic function in NG108-15 neuroblastoma x ***glioma*** hybrid cells.
AU Higashida H; Yokoyama S; Hoshi N; Myojo Y; Kawamura T; Ito Y; Hashii M; Sagara J; Furuya K
CS Department of Biophysics, Kanazawa University School of Medicine, Japan.
SO COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY. C: COMPARATIVE PHARMACOLOGY AND TOXICOLOGY, (1991) 98 (1) 129-37. Ref: 48
Journal code: DNX; 8310013. ISSN: 0742-8413.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199106
ED Entered STN: 19910630
Last Updated on STN: 19970203
Entered Medline: 19910613
AB 1. The second-messengers system of ***bradykinin*** (BK) receptors was examined in NG108-15 neuroblastoma x ***glioma*** hybrid cells. 2. An application of BK induced an immediate outward (K+) current and acetylcholine (ACh) release, which are generated through inositol 1,4,5-trisphosphate (InsP3)-dependent Ca2+ ions. 3. Application of phorbol dibutyrate (a protein kinase C activator) produced a voltage-dependent inward current and inhibited another K+ (M)-current. 4. A similar current response has been produced by ACh in NG108-15 cells transfected with rodent muscarinic ACh receptor I and III subtype genes. 5. These results suggest a dual and time-dependent role for these two intracellular messengers in the control of neuronal signalling by BK and ACh.

L15 ANSWER 29 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 11
AN 1990:135313 BIOSIS
DN BA89:74124
TI ACTIVATION OF POTASSIUM CONDUCTANCE BY ***BRADYKININ*** AND BY INOSITOL 1 4 5-TRISPHOSPHATE IN RAT ***GLIOMA*** CELLS INVOLVEMENT OF

INTRACELLULAR AND EXTRACELLULAR CALCIUM.
AU REISER G; BINMOELLER F-J; STRONG P N; HAMPRECHT B
CS PHYSIOLOGISCH-CHEMISCHES INST., UNIV. TUEBINGEN, HOPPE-SEYLER-STR. 4, 7400
TUEBINGEN, FRG.
SO BRAIN RES, (1990) 506 (2), 205-214.
CODEN: BRREAP. ISSN: 0006-8993.
FS BA; OLD
LA English
AB Extracellular application of ***bradykinin*** and injection of inositol-1,4,5-trisphosphate (Ins-P3) induced a hyperpolarization in polyploid rat ***glioma*** cells. Ins-1,4,5-P3 and Ins-2,4,5-P3 were effective but not Ins-4,5-P2, Ins-1,3,4,5-P4 and Ins-1,3,4,5,6-P5. The reversal potential of the hyperpolarizing response induced by ***bradykinin*** or by Ins-P3 increased to a comparable degree with increasing the extracellular K+ concentration. Certain blockers of ***K*** + ***channels*** , for example charybdotoxin (5-50 mM), Ba2+ (5-20 mM), 4-aminopyridine (5-10 mM) and quinidine (0.1-0.5 mM) reversibly suppressed the membrane potential response to ***bradykinin*** or to Ins-P3; however, apamin (1 .mu.M) and D-tubocurarine (0.5 mM) had no effect. Intracellular injection of EGTA made the ***glioma*** cells unresponsive to ***bradykinin*** . Superfusion of the cells with Ca2+-free medium gradually and reversibly abolished the response to ***bradykinin*** , but only slightly reduced the effect of Ins-P3. The Ca2+ channel blockers Co2+ (1-5 mM), Mn2+ (2-6 mM) and nifedipine (1-20 .mu.M), but not desmethoxyverapamil (100 .mu.M) inhibited the hyperpolarizing effect of ***bradykinin*** . The hyperpolarization induced by Ins-P3, however, was not influenced by Mn2+ (1-5 mM) or by Co2+ (7 mM). Injection of Ca2+ into the ***glioma*** cells induced a hyperpolarization susceptible to Ba2+ and quinidine. Treatment of ***glioma*** cells with an activator or with inhibitors of protein kinase C or with pertussis toxin did not affect the response to ***bradykinin*** . Incubation of the cells with the Ca2+ ionophore A23187 (0.1-1 .mu.M) made the cells unresponsive to ***bradykinin*** and, somewhat less, to Ins-P3. At these concentrations the Ca2+ ionophore primarily depletes intracellular Ca2+ stores. In summary, ***bradykinin*** , via B2-receptors (blocked by [Thi5,8, D-Phe7]-***bradykinin***) activates a K+ conductance in ***glioma*** cells following a rise of cytosolic Ca2+ activity most likely due to Ins-P3-mediated release of Ca2+ from internal stores. Entry of extracellular Ca2+ appears also to be involved in this process.

L15 ANSWER 30 OF 37 MEDLINE
AN 89327252 MEDLINE
DN 89327252 PubMed ID: 2787795
TI The effect of epidermal growth factor on membrane potential. Rapid hyperpolarization followed by persistent fluctuations.
AU Pandiella A; Magni M; Lovisolo D; Meldolesi J
CS Department of Pharmacology, University of Milano, Italy.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1989 Aug 5) 264 (22) 12914-21.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198909
ED Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19890907
AB The effects of epidermal growth factor (EGF) on membrane potential were investigated in suspensions of the following three cell types endowed with a large complement of specific receptors: EGFR-T17 (a clone of mouse NIH-3T3 fibroblasts overexpressing EGF receptors); A431 and KB (two human carcinoma lines). In all these lines EGF induced a rapid and marked hyperpolarization constituted by an initial peak (in all three cell lines) and a subsequent sustained plateau phase, concomitant with the well-known increase of [Ca2+]i. The time course and phorbol ester inhibitability of the membrane potential effects were the same as for the [Ca2+]i response. Experiments with Na+-free and chloride-free media excluded a major role of the latter ions in the EGF-induced hyperpolarization. In contrast, experiments with high K+ media, with the monovalent cation ionophore gramicidin and with Ca2+-free media together with either a Ca2+ ionophore (ionomycin, in A431 and EGFR-T17), or an agonist (***bradykinin*** , in A431) addressed to a receptor coupled to phosphoinositide hydrolysis, were consistent with the involvement of Ca2+-activated ***K*** + ***channels*** . The EGF-induced hyperpolarization was completely blocked by the ***K*** + ***channel*** blocker, quinidine, and unaffected by a variety of other drugs. Patch clamping of individual EGFR-T17 cells confirmed the initial hyperpolarization (from approximately -30 mV, the resting potential, to -60, -80 mV) was due to activation of an outward current. This initial hyperpolarization was followed by fluctuations (period approximately 1 min) persisting as long as the cells could be analyzed. Thus, the changes of membrane potential appear to be not only novel members of the group of early events triggered by EGF in target cells but also long-lasting effects of the growth factor, which continue for unexpectedly long periods of time after EGF application.

L15 ANSWER 31 OF 37 MEDLINE
AN 90005971 MEDLINE
DN 90005971 PubMed ID: 2792371
TI ***Bradykinin*** inhibits a potassium M-like current in rat pheochromocytoma PC12 cells.
CM Erratum in: FEBS Lett 1990 Feb 12;261(1):217
AU Villarroel A; Marrion N V; Lopez H; Adams P R
CS Howard Hughes Medical Institute, Department of Neurobiology and Behavior, SUNY, Stony Brook 11794-5230.
SO FEBS LETTERS, (1989 Sep 11) 255 (1) 42-6.
Journal code: EUH; 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198911
ED Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891109
AB We studied the action of ***bradykinin*** (BK) on ionic currents in fused pheochromocytoma PC12 cells under voltage-clamp in whole-cell mode, and on intracellular calcium using fura-2 BK induced the development of an outward current associated with an increase in intracellular calcium, followed by inhibition of an M-like current. The outward current was blocked by (+)-tubocurarine, and prevented when the calcium BAPTA or high concentrations of inositol 1,4,5-triphosphate were introduced into the cell, whereas the M-like current and its inhibition by BK remained unaffected. The protein kinase activator phorbol 12,13 dibutyrate partially reduced the M-current. M-current density did not substantially change after prolonged treatment with nerve growth factor.

L15 ANSWER 32 OF 37 MEDLINE DUPLICATE 12
AN 89005721 MEDLINE
DN 89005721 PubMed ID: 3262538
TI Ca2+-dependent ***K*** + ***channels*** in neuroblastoma hybrid cells activated by intracellular inositol trisphosphate and extracellular ***bradykinin*** .
AU Higashida H; Brown D A
CS Laboratory of Biochemical Genetics, National Heart, Lung and Blood Institute, Bethesda, MD 20892.
SO FEBS LETTERS, (1988 Oct 10) 238 (2) 395-400.
Journal code: EUH; 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198811
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881114
AB ***Bradykinin*** (BK) activation of phosphatidylinositide breakdown in NG108-15 neuroblastoma x ***glioma*** hybrid cells in the generation of an outward K+ current through the release of Ca2+ by the intermediary messenger inositol 1,4,5-trisphosphate (InsP3). Channels mediating this outward current were identified using cell-attached patch electrodes. Intracellular iontophoretic injection of InsP3 or Ca2+, or extracellular application of BK, evoked bursts of ***K*** + ***channel*** activity coincident with cell hyperpolarization measured with an intracellular recording micropipette. The most frequent channels had a mean single-channel conductance of about 40 pS in symmetrical K+ solutions; additional openings of lower conductance (18 pS) channels were also detected. Bath application of phorbol dibutyrate (PDBu, 1 microM) increased the number and opening probability of the InsP3-induced channels.

L15 ANSWER 33 OF 37 MEDLINE
AN 89337487 MEDLINE
DN 89337487 PubMed ID: 2855484
TI Role of G-protein-coupled phosphatidylinositide system in signal transduction in vertebrate neurons: experiments on neuroblastoma hybrid cells and ganglion cells.
AU Brown D A; Higashida H; Adams P R; Marrion N V; Smart T G
CS Department of Pharmacology, University College London, United Kingdom.
NC NS-18579 (NINDS)
SO COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, (1988) 53 Pt 1
375-84.
Journal code: DMT; 1256107. ISSN: 0091-7451.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198909
ED Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19890915

L15 ANSWER 34 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 1988:225623 BIOSIS
DN BA85:114858
TI MEMANTINE 1 AMINO-3 5-DIMETHYLADAMANTANE BLOCKS THE SEROTONIN-INDUCED
DEPOLARIZATION RESPONSE IN A NEURONAL CELL LINE.
AU REISER G; BINMOELLER F-J; KOCH R
CS PHYSIOL.-CHEM. INST. UNIV. TUEBINGEN, HOPPE-SEYLER-STR. 4, 7400 TUEBINGEN,
F.R.G.

SO BRAIN RES, (1988) 443 (1-2), 338-344.
CODEN: BRREAP. ISSN: 0006-8993.
FS BA; OLD
LA English
AB The influence of memantine on several properties of a neuronal cell line was tested. The aim was to get some insight into possible mechanisms of action of this drug which is therapeutically applicable in treatment of spasticity. Parkinson's disease, and cerebral coma. In neuroblastoma .times. ***glioma*** hybrid cells, memantine, at micromolar concentrations, blocked the depolarization induced by iontophoretically applied serotonin (5-hydroxytryptamine, 5-HT). In the hybrid cells, receptors of the 5-HT3 type mediated the depolarization, which was frequently accompanied by a series of action potentials. The inhibition by memantine of the serotonin response occurred fast and was completely reversible, irrespective of whether the cell showed a stable membrane potential or spontaneous action potentials. However, memantine did not alter spontaneous or electrically evoked action potential activity in the hybrid cells, and apparently did not block the underlying ionic conductances. Furthermore memantine did not affect either the cation permeability activated by substances P in the hybrid cells or the ***K*** + ***channel*** triggered by ***bradykinin*** in a ***glioma*** cell line. Thus, memantine appears specifically to suppress the ion channel opened by serotonin in the hybrid cells. The interaction of memantine with serotonin receptors and the associated ion channels reported here, might gave an important clue, as to a site of action of memantine in the nervous system.

L15 ANSWER 35 OF 37 MEDLINE
AN 88134134 MEDLINE
DN 88134134 PubMed ID: 2449200
TI The regulatory influence of ***bradykinin*** and inositol-1,4,5-trisphosphate on the membrane potential in neural cell lines.
AU Reiser G; Binmoller F J; Hamprecht B
CS Physiologisch- Chemisches Institut der Universitat Tubingen, F.R.G.
SO BIOMEDICA BIOCHIMICA ACTA, (1987) 46 (8-9) S682-7.
Journal code: 9YX; 8304435. ISSN: 0232-766X.
CY GERMANY, EAST: German Democratic Republic
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198803
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880315
AB The effect of ***bradykinin*** on membrane potential, level of cyclic nucleotides and of cytosolic Ca2+-activity was determined in neural cell lines. ***Bradykinin*** induced a transient hyperpolarization followed by a depolarization in mouse neuroblastoma x rat ***glioma*** hybrid cells and in polyploid rat ***glioma*** cells. The reversal potential of the hyperpolarizing response depended on the extracellular K+ concentration. The ***K*** + ***channel*** blockers, Ba2+, quinidine, and 4-aminopyridine, inhibited the response to ***bradykinin*** . This suggests that the hyperpolarization of ca. 1 min duration, which was accompanied by a decreased input resistance, is due to activation of ***K*** + ***channels*** . Upon addition of ***bradykinin*** to the cells the cytosolic Ca2+-activity increased transiently. Ca2+ was involved in the induction of the hyperpolarization by ***bradykinin*** , since both removal of extracellular Ca2+ and injection of EGTA into the cells suppressed the membrane potential response. ***Bradykinin*** induced the formation of inositol-1,4,5-trisphosphate (IP3), an agent known to release Ca2+ from intracellular stores, and stimulated the uptake of 45Ca2+ into the cells. Therefore the increased level of intracellular Ca2+ activating the K+ conductance could be due to two components: release from intracellular pools and uptake. IP3 seems to be involved in the membrane potential response, because intracellular injection of either IP3 or Ca2+ into the ***glioma*** cells elicited a hyperpolarizing response which resembled that after application of ***bradykinin*** and was also susceptible to the ***K*** + ***channel*** blocking agents listed above. However, the formation of cyclic GMP by ***bradykinin*** apparently plays no role in the membrane potential effect of ***bradykinin*** .

L15 ANSWER 36 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
AN 1987:191678 BIOSIS
DN BA83:99802
TI ATRIAL NATRIURETIC POLYPEPTIDE HORMONES INDUCE MEMBRANE POTENTIAL
RESPONSES IN CULTURED RAT ***GLIOMA*** CELLS.
AU REISER G; HOPP H-P; HAMPRECHT B
CS PHYSIOLOGISCH-CHEMISCHES INST., UNIV. TUEBINGEN, HOPPE-SEYLER-STR. 4,
D-7400 TUEBINGEN, FRG.
SO BRAIN RES, (1987) 402 (1), 164-167.
CODEN: BRREAP. ISSN: 0006-8993.
FS BA; OLD
LA English
AB Atrial natriuretic hormones (ANHs) applied to polyploid rat ***glioma*** cells induced hyperpolarizations of about 30 s duration, followed by depolarizations lasting 1-2 min. Repeated applications of the peptide resulted in desensitization. The reversal potential of -87 mV at an extracellular K+ concentration of 5 mM and the decrease of membrane resistance during the hyperpolarization indicate that ***K*** + ***channels*** were activated by ANH. In these cells the fluorescence signal of 2-[(2-bis[carboxymethyl]amino-5-methylphenoxy)-methyl]-6-methoxy-8-bis[carboxymethyl]aminoquinoline (quin2) was not affected by ANH suggesting that ANH did not change the cytosolic Ca2+-activity.

L15 ANSWER 37 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
15
AN 1986:209577 BIOSIS
DN BA81:100877
TI ***BRADYKININ*** -ACTIVATED TRANSMEMBRANE SIGNALS ARE COUPLED VIA
GUANINE NUCLEOTIDE-BINDING PROTEINS TO PRODUCTION OF INOSITOL 1 4
5-TRISPHOSPHATE A SECOND MESSENGER IN NG-108-15 NEUROBLASTOMA-
GLIOMA HYBRID CELLS.
AU HIGASHIDA H; STREATY R A; KLEE W; NIRENBERG M
CS LAB. BIOCHEMICAL GENETICS, NATIONAL HEART, LUNG AND BLOOD INST., NATIONAL
INST. HEALTH, BETHESDA, MD 20892.
SO PROC NATL ACAD SCI U S A, (1986) 83 (4), 942-946.
CODEN: PNASA6. ISSN: 0027-8424.
FS BA; OLD
LA English
AB The addition of ***bradykinin*** to NG108-15 cells results in a transient hyperpolarization followed by prolonged cell depolarization. Injection of inositol 1,4,5-triphosphate or Ca2+ into the cytoplasm of NG108-15 cells also elicits cell hyperpolarization followed by depolarization. Tetraethylammonium ions inhibit the hyperpolarizing response of cells to ***bradykinin*** or inositol 1,4,5-trisphosphate. Thus, the hyperpolarizing phase of the cell response may be due to inositol 1,4,5-trisphosphate-dependent release of stored Ca2+ into the cytoplasm, which activates Ca2+-dependent ***K*** + ***channels*** . The depolarizing phase of the cell response to ***bradykinin*** is due largely to inhibition of M channels, thereby decreasing the rate of K+ efflux from cells and, to a lesser extent, to activation Ca2+-dependent ion channels and Ca2+ channels. In contrast, injection of inositol 1,4,5-trisphosphate or Ca2+ into the cytosol did not alter M channel activity. Incubation of NG108-15 cells with pertussis toxin inhibits ***bradykinin*** -dependent cell hyperpolarization and depolarization. ***Bradykinin*** stimulates low Km GTPase activity and inhibits adenylate cyclase in NG108-15 membrane preparations but not in membranes prepared from cells treated with pertussis toxin. Reconstitution of NG108-15 membranes from cells treated with pertussis toxin with nanomolar concentrations of a mixture of highly purified No and Ni [guanine nucleotide-binding proteins that have no known function (No) or inhibit adenylate cyclase (Ni)] restores ***bradykinin*** -dependent activation of GTPase and inhibition of adenylate cyclase. These results show that [***bradykinin*** -receptor] complexes interact with No or Ni and suggest that No and/or Ni mediate the tansduction of signals from ***bradykinin*** receptors to phospholipase C and adenylate cyclase.

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NEWS 4 Feb 01 DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5 Feb 19 Access via Tymnet and SprintNet Eliminated Effective 3/31/02

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NEWS 8 Mar 22 TRCTHERMO no longer available
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=> s BK channel
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=> s BK channels
L2 726 BK CHANNELS

=> s l1 or l2
L3 929 L1 OR L2

=> s l3 and drug deliver?
L4 0 L3 AND DRUG DELIVER?

=> s l3 and soluble guanylyl cyclase
L5 0 L3 AND SOLUBLE GUANYLYL CYCLASE

=> s soluble guanylyl cyclase?
L6 1927 SOLUBLE GUANYLYL CYCLASE?

=> s l6 and l3
L7 0 L6 AND L3

=> s l6 and drug deliver
L8 0 L6 AND DRUG DELIVER

=> s l6 and drug deliver?
L9 1 L6 AND DRUG DELIVER?

=> d bib abs

L9 ANSWER 1 OF 1 MEDLINE
AN 95007696 MEDLINE
DN 95007696 PubMed ID: 7923298
TI Long term increases in coronary arterial conductance during five day infusion of low dose nicorandil.
AU Bassenge E; Fink B; Sommer O; Huckstorf C
CS University of Freiburg, Department of Applied Physiology, Germany.
SO CARDIOVASCULAR RESEARCH, (1994 Jun) 28 (6) 912-6.
Journal code: COR; 0077427. ISSN: 0008-6363.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199410
ED Entered STN: 19941222
Last Updated on STN: 19990129
Entered Medline: 19941024
AB OBJECTIVE: The aim was to test the effects of nicorandil on coronary arterial conductance and on a possible development of tolerance or cross tolerance with glyceryl trinitrate during a 5 d continuous intravenous infusion of this hybrid molecule (consisting of a combination of potassium channel activation and simultaneous nitro-ester induced ***soluble*** ***guanylyl*** - ***cyclase*** activation). METHODS: Continuous intravenous infusions of nicorandil at 2.5 micrograms.kg-1.min-1 and 10 micrograms.kg-1.min-1 into conscious chronically instrumented dogs were carried out for 5 d using a special portable infusion system. Employing additional short term infusions, dose-response curves were obtained by giving nicorandil or glyceryl trinitrate at increasing dosages both in the preinfusion control state and 4 h after terminating the nicorandil infusion. RESULTS: The 5 d infusion of 2.5 or 10.0 micrograms.kg-1.min-1 nicorandil resulted in a significant increase in large coronary artery diameter by 4.21 (SEM 0.14)% or 9.20(0.28)%, respectively. At the lower dose no significant tolerance or cross tolerance with glyceryl trinitrate was observed. However, at the higher dose there was a shift of the dose-response curve of both nicorandil and glyceryl trinitrate to the right, indicating some tolerance. The smaller dose did not induce hypotension or reflex increase in heart rate, whereas the larger resulted in a 42(2.5)% increase in heart rate. CONCLUSIONS: A dose regimen of 2.5 micrograms.kg-1.min-1 continuously administered for 5 d is capable of inducing a significant increase in coronary arterial conductance which was well maintained over the whole infusion period. Thus nicorandil can exert a selective large coronary artery dilatation and may bring about a well maintained increase in epicardial coronary conductance, especially when applied as a low dose slow release preparation which circumvents hypotension and increase in heart rate.

=> s l6 and (tumor or cancer or glioma)
L10 61 L6 AND (TUMOR OR CANCER OR GLIOMA)

=> s l6 and blood brain barrier?
L11 1 L6 AND BLOOD BRAIN BARRIER?

=> d bib abs

L11 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:488296 BIOSIS
DN PREV199598502596
TI Contributions of NO synthase and heme oxygenase to cGMP formation by cytokine and hemin treated brain capillary endothelial cells.
AU Vigne, Paul; Feolde, Erick; Ladoux, Annie; Duval, Daniele; Frelin, Christian (1)
CS (1) Inst. de Pharmacologie Moleculaire et Cellulaire du CNRS, Univ. de Nice-Sophia Antipolis, 660 route des Lucioles, 06530 Valbonne France
SO Biochemical and Biophysical Research Communications, (1995) Vol. 214, No. 1, pp. 1-5.
ISSN: 0006-291X.
DT Article
LA English
AB Two mechanisms contribute to cGMP formation by ***soluble*** ***guanylyl*** ***cyclase*** (i) NO production by NO synthase and (ii) CO production by heme oxygenase. We analyze here the contributions of these two pathways to IL1, TNF, lipopolysaccharide and hemin treated brain capillary endothelial cells. Cytokines and LPS induced cGMP formation in manners that were completely prevented by LY 83,583, methylene blue and by cyclosporin A. They were partially inhibited by inhibitors of NO synthase. Cyclosporin A acts by a posttranscriptional mechanism. Cells constitutively expressed mRNAs for heme oxygenase-1. Expression was enhanced by hemin but not by IL1 or lipopolysaccharide. Induction of heme oxygenase-1 and its inhibition by Sn protoporphyrin IX had no effect on cGMP levels.

=> dup rem l10
PROCESSING COMPLETED FOR L10
L12 31 DUP REM L10 (30 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 31 ANSWERS - CONTINUE? Y/(N):y

L12 ANSWER 1 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2002:192321 BIOSIS
DN PREV200200192321
TI Zaprinast, an inhibitor of cGMP-selective phosphodiesterases, enhances the secretion of TNF-alpha and IL-1beta and the expression of iNOS and MHC class II molecules in rat microglial cells.
AU Choi, Sang-Hyun; Choi, Dong-Hee; Song, Kwang-Seon; Shin, Kyung-Ho; Chun,

Boe-Gwun (1)
CS (1) Department of Pharmacology, Korea University College of Medicine, 126-1, 5-Ga, Anam-Dong, Sungbuk-Gu, Seoul, 136-705: shchoi@korea.ac.kr South Korea
SO Journal of Neuroscience Research, (February 1, 2002) Vol. 67, No. 3, pp. 411-421. http://www.interscience.wiley.com/jpages/0360-4012/. print.
ISSN: 0360-4012.
DT Article
LA English
AB Proinflammatory cytokines produced by activated glial cells may in turn augment the immune/inflammatory reactions of glial cells through autocrine and paracrine routes. The NO/cGMP signaling represents one of the reactions of activated glial cells. We investigated whether the production of proinflammatory cytokines by glial cells is affected by NO-dependent downstream cGMP signaling. In primary cultures of mixed astrocytes and microglial cells, zaprinast (0.1 mM), an inhibitor of cGMP-selective phosphodiesterases, enhanced the basal and LPS (1.0 mug/ml)-induced secretion of TNF-alpha and IL-1beta. Zaprinast also enhanced NO production induced by LPS or IFN-gamma (100 U/ml), and in microglial cell cultures, but not in astrocyte cultures, zaprinast enhanced the basal and the IFN-gamma-induced production of the cytokines, TNF-alpha and IL-1beta, and of NO. This upregulation by zaprinast was partially inhibited by KT5823 (1.0 muM), an inhibitor of protein kinase G. The LPS-induced production of TNF-alpha, IL-1beta, and NO was inhibited by ODQ (50 muM), an inhibitor of ***soluble*** ***guanylyl*** ***cyclase*** , and by KT5823. Immunohistochemical analysis of mixed glial cell cultures showed that LPS/IFN-gamma-induced iNOS expression and the enhanced expression of iNOS by zaprinast were restricted to microglial cells. Zaprinast enhanced the IFN-gamma (200 U/ml)-induced expression of MHC Class II molecules in astrocytes and microglial cells in mixed cultures, but did not enhance this IFN-gamma-induced expression in pure astrocytes, which lacked paracrine TNF-alpha from microglial cells. Summarizing, zaprinast, which is associated with cGMP/protein kinase G signaling, may augment central immune/inflammatory reactions, possibly via the increased production of TNF-alpha and IL-1beta by activated microglial cells.

L12 ANSWER 2 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2002:149745 BIOSIS
DN PREV200200149745
TI Nitric oxide suppresses the expression of Bcl-2 binding protein BNIP3 in hepatocytes.
AU Zamora, Ruben (1); Alarcon, Louis; Vodovotz, Yoram; Betten, Binnie; Kim, Peter K. M.; Gibson, Kevin F.; Billiar, Timothy R.
CS (1) Dept. of Pediatric Surgery, Rangos Research Center (CHP), 3705 Fifth Ave., Rm. 8125, Pittsburgh, PA, 15213: zamorar@pitt.edu USA
SO Journal of Biological Chemistry, (December 14, 2001) Vol. 276, No. 50, pp. 46887-46895. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Nitric oxide (NO) is not only an important signaling molecule, but it also regulates the expression of a number of genes in the liver. We have previously shown that apoptosis in hepatocytes exposed to ***tumor*** necrosis factor-alpha and actinomycin D is prevented by NO derived from the inducible nitric-oxide synthase (iNOS), by mechanisms that are both dependent on and independent of modulation of cyclic guanosine monophosphate (cGMP) subsequent to activation of ***soluble*** ***guanylyl*** ***cyclase*** (sGC). We hypothesize that one mechanism by which NO exerts these effects is by regulating the expression of genes involved in apoptosis. We used differential display-polymerase chain reaction to isolate NO-regulated genes in hepatocytes from iNOS knockout mice (to eliminate endogenous inducible NO production). Using this analysis, we identified a NO-suppressed gene fragment homologous with the pro-apoptotic Bcl-2 binding protein BNIP3. Northern analysis confirmed the NO-dependent suppression of BNIP3 in cultured cells. Similarly, the NO donor S-nitroso-N-acetyl-DL-penicillamine (1-1000 muM) down-regulated the expression of BNIP3 in both iNOS knockout and wild-type hepatocytes. This effect of NO was reversed by the sGC inhibitor 1H-(1,2,4)-oxadiazole(4,3-a)quinoxalon-1-one (ODQ), suggesting the involvement of the sGC/cGMP pathway in the modulation of BNIP3 by NO. We propose that suppression of BNIP3 expression is one sGC/cGMP-dependent mechanism by which NO might affect the process of hepatocyte apoptosis.

L12 ANSWER 3 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:278497 BIOSIS
DN PREV200100278497
TI Spontaneous and receptor-controlled ***soluble*** ***guanylyl*** ***cyclase*** activity in anterior pituitary cells.
AU Kostic, Tatjana S.; Andric, Silvana A.; Stojilkovic, Stanko S. (1)
CS (1) Section on Cellular Signaling, Endocrinology and Reproduction Research Branch, National Institute of Child Health and Human Development, 49 Convent Drive, Building 49, Room 6A-36, Bethesda, MD, 20892-4510: stankos@helix.nih.gov USA
SO Molecular Endocrinology, (June, 2001) Vol. 15, No. 6, pp. 1010-1022. print.
ISSN: 0888-8809.
DT Article
LA English
SL English
AB Nitric oxide (NO)-dependent ***soluble*** ***guanylyl*** ***cyclase*** (sGC) is operative in mammalian cells, but its presence and the role in cGMP production in pituitary cells have been incompletely characterized. Here we show that sGC is expressed in pituitary tissue and dispersed cells, enriched lactotrophs and somatotrophs, and GH3 immortalized cells, and that this enzyme is exclusively responsible for cGMP production in unstimulated cells. Basal sGC activity was partially dependent on voltage-gated calcium influx, and both calcium-sensitive NO synthases (NOS), neuronal and endothelial, were expressed in pituitary tissue and mixed cells, enriched lactotrophs and somatotrophs, and GH3 cells. Calcium-independent inducible NOS was transiently expressed in cultured lactotrophs and somatotrophs after the dispersion of cells, but not in GH3 cells and pituitary tissue. This enzyme participated in the control of basal sGC activity in cultured pituitary cells. The overexpression of inducible NOS by lipopolysaccharide + interferon-gamma further increased NO and cGMP levels, and the majority of de novo produced cGMP was rapidly released. Addition of an NO donor to perifused pituitary cells also led to a rapid cGMP release. Calcium-mobilizing agonists TRH and GnRH slightly increased basal cGMP production, but only when added in high concentrations. In contrast, adenylyl cyclase agonists GHRH and CRF induced a robust increase in cGMP production, with EC50s in the physiological concentration range. As in cells overexpressing inducible NOS, the stimulatory action of GHRH and CRF was preserved in cells bathed in calcium-deficient medium, but was not associated with a measurable increase in NO production. These results indicate that sGC is present in secretory anterior pituitary cells and is regulated in an NO-dependent manner through constitutively expressed neuronal and endothelial NOS and transiently expressed inducible NOS, as well as independently of NO by adenylyl cyclase coupled-receptors.

L12 ANSWER 4 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:261452 BIOSIS
DN PREV200100261452
TI N-acetylcysteine inhibits nitric oxide induced degeneration of SH-SY5Y human neuroblastoma cells.
AU Meij, Johanna T. A. (1); Haselton, Carole L. (1); Ebadi, Manuchair (1)
CS (1) University of North Dakota, 501 N. Columbia Road, Grand Forks, ND, 58203-2817 USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A932. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Nitric oxide (NO) in the brain originates from astroglial cells stimulated by inflammatory factors to express inducible NO synthase (NOS), and neurons expressing neuronal NOS coupled to ionotropic glutamate receptors. NO targets cellular proteins like ***soluble*** ***guanylyl*** ***cyclase*** (sGC) and metallothionein, but can also form radical species, most notably peroxynitrite. Various findings implicate NO in the loss of dopamine neurons as seen in Parkinson's disease. We compared the effects of NO in the human dopaminergic neuroblastoma, SH-SY5Y, and the human neuroblastoma X mouse ***glioma*** , NG108-15, cell lines. In both cell types incubation with NO donors, diethylenetetraamine (DETA) NONOate and linsidomine (SIN-1), evoked a dose-dependent increase in sGC activity, as determined by cGMP radioimmunoassay. As well, NO donors induced a dose-dependent decrease in number of viable cells, as determined by luminescent ATP detection assay after 24 h. The EC50 of DETA NONOate (t1/2=20 h) was 0.12 and 2.1 mM in SH-SY5Y and NG108-15 cells, respectively. SH-SY5Y cells were also more susceptible to SIN-1 induced cell degeneration than NG108-15 cells. To find out pathways involved in NO induced SH-SY5Y cell degeneration, various inhibitors were applied. The sGC inhibitor, 1H-(1,2,4)oxadiaz-olo(4,3-a)quinoxalin-1-one, and the poly(ADP-ribose) polymerase (PARP) inhibitor, 3-aminobenzamide, did not affect NO donor induced cell degeneration, ruling out cGMP- or PARP-dependent apoptotic pathways. The presence of N-acetylcysteine, either during incubation or 18 h pre-incubation, dose-dependently inhibited the NO induced decrease in SH-SY5Y cell viability. N-Acetylcysteine may prevent modification and/or depletion of intracellular thiols by NO induced redox stress.

L12 ANSWER 5 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
AN 2001:335945 BIOSIS
DN PREV200100335945
TI Posttranscriptional regulation of human iNOS by the NO/cGMP pathway.
AU Perez-Sala, Dolores (1); Cernuda-Morollon, Eva; Diaz-Cazorla, Manuela; Rodriguez-Pascual, Fernando; Lamas, Santiago
CS (1) Centro de Investigaciones Biologicas, CSIC, Velazquez, 144, 28006, Madrid: dperezsala@cib.csic.es Spain
SO American Journal of Physiology, (March, 2001) Vol. 280, No. 3 Part 2, pp. F466-F473. print.
ISSN: 0002-9513.
DT Article
LA English
SL English
AB Nitric oxide (NO) and cGMP may exert positive or negative effects on inducible NO synthase (iNOS) expression. We have explored the influence of the NO/cGMP pathway on iNOS levels in human mesangial cells. Inhibition of

NOS activity during an 8-h stimulation with IL-1beta plus ***tumor*** necrosis factor (TNF)-alpha reduced iNOS levels, while NO donors amplified iNOS induction threefold. However, time-course studies revealed a subsequent inhibitory effect of NO donors on iNOS protein and mRNA levels. This suggests that NO may contribute both to iNOS induction and downregulation. ***Soluble*** ***guanylyl*** ***cyclase*** (sGC) activation may be involved in these effects. Inhibition of sGC attenuated IL-1beta/TNF-alpha-elicited iNOS induction and reduced NO-driven amplification. Interestingly, cGMP analogs also modulated iNOS protein and mRNA levels in a biphasic manner. Inhibition of transcription unveiled a negative post-transcriptional modulation of the iNOS transcript by NO and cGMP at late times of induction. Supplementation with 8-bromo-cGMP (8-BrcGMP) reduced iNOS mRNA stability by 50%. These observations evidence a complex feedback regulation of iNOS expression, in which posttranscriptional mechanisms may play an important role.

L12 ANSWER 6 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2001:174377 BIOSIS
DN PREV200100174377
TI Differential expression of functional guanylyl cyclases in melanocytes: Absence of nitric-oxide-sensitive isoform in metastatic cells.
AU Ivanova, Krassimira (1); Das, Pranab K.; van den Wijngaard, Rene M. J. G. J.; Lenz, Wolfgang; Klockenbring, Torsten; Malcharzyk, Vanessa; Drummer, Christian; Gerzer, Rupert
CS (1) Institute of Aerospace Medicine, German Aerospace Center, Linder Hoehe, 51170, Cologne: krassimira.ivanova@dlr.de Germany
SO Journal of Investigative Dermatology, (March, 2001) Vol. 116, No. 3, pp. 409-416. print.
ISSN: 0022-202X.
DT Article
LA English
SL English
AB Nitric oxide (NO) is a reactive endogenous molecule with multiple functions and its cellular signaling activity is mainly mediated by activation of the soluble isoform of guanylyl cyclase, a heterodimeric (alpha/beta) hemeprotein. The expression of the NO-sensitive soluble isoform of guanylyl cyclase was studied in various cultured melanocytic cells by measuring the accumulation of guanosine 3',5'-cyclic monophosphate in the presence and absence of NO donors. Here we report that 3-morpholino-sydnonimine, a donor of NO redox species, and (Z)-1-(2-(2-aminoethyl)-N-(2-ammonioethyl)amino)diazen-1-ium-1,2-diolate, a direct NO donor, induced a 20-fold increase in intracellular guanosine 3',5'-cyclic monophosphate in nonmetastatic melanoma cells and normal melanocytes in culture that could be related to cellular melanin content in a concentration-dependent manner. The increased intracellular guanosine 3',5'-cyclic monophosphate was due to stimulation of the activity of ***soluble*** ***guanylyl*** ***cyclase*** as such increase was completely abolished by using a specific inhibitor of ***soluble*** ***guanylyl*** ***cyclase*** . The involvement of functional ***soluble*** ***guanylyl*** ***cyclase*** was further confirmed by the presence of alpha1 and beta1 subunits in these cells at both mRNA and protein levels. In contrast, none of the NO donors induced guanosine 3',5'-cyclic monophosphate production in metastatic melanoma cells, which could be attributed to the absence of the beta1 subunit that is essential for catalytic activity of the soluble isoform of guanylyl cyclase. Metastatic melanoma cells produced higher levels of intracellular guanosine 3',5'-cyclic monophosphate in response to natriuretic peptides than other cell types, however, due to upregulation of membrane-bound guanylyl cyclase activities, but they are less pigmented or unpigmented. The present finding suggests that NO signaling in association with melanogenesis is dependent on the soluble isoform of guanylyl cyclase, whereas absence of ***soluble*** ***guanylyl*** ***cyclase*** but the presence of membrane-bound guanylyl cyclase correlates with the metastatic behavior of melanoma cells.

L12 ANSWER 7 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2001:81155 BIOSIS
DN PREV200100081155
TI Matrix metalloproteinase 2 in ***tumor*** cell-induced platelet aggregation: Regulation by nitric oxide.
AU Jurasz, Paul; Sawicki, Grzegorz; Duszyk, Marek; Sawicka, Jolanta; Miranda, Carlos; Mayers, Irvin; Radomski, Marek W. (1)
CS (1) University of Alberta, 9-50 Medical Sciences Building, Edmonton, AB, T6G 2H7: Marek.Radomski@Ualberta.CA Canada
SO Cancer Research, (January 1, 2001) Vol. 61, No. 1, pp. 376-382. print.
ISSN: 0008-5472.
DT Article
LA English
SL English
AB A correlation exists between the ability of ***tumor*** cells to aggregate platelets and their tendency to metastasize. ***Tumor*** cell-induced platelet aggregation (TCIPA) facilitates the embolization of the vasculature with ***tumor*** cells and the formation of metastatic foci. It is well documented that matrix metalloproteinases (MMPs) play an integral part in ***tumor*** spread and the metastatic cascade. Therefore, we have examined the role of MMPs during TCIPA and its regulation by nitric oxide (NO) in vitro. Human HT-1080 fibrosarcoma and A549 lung epithelial ***cancer*** cells induced TCIPA in a concentration-dependent manner that was monitored by aggregometry. This aggregation resulted in the release of MMP-2 from platelets and ***cancer*** cells, as measured by zymography. HT-1080 cells released significantly more MMP-2 than A549 cells and were more efficacious in inducing TCIPA. Inhibition of MMP-2 with phenanthroline (1-1000 muM), a synthetic inhibitor of MMPs, and by neutralizing anti-MMP-2 antibody (10 mug/ml) reduced TCIPA induced by HT-1080 cells. TCIPA was abolished by simultaneous inhibition of platelet function with acetylsalicylic acid (100 muM; thromboxane pathway inhibitor), apyrase (250 mug/ml; ADP pathway inhibitor), and phenanthroline. NO donors such as S-nitroso-n-acetylpenicillamine and S-nitrosoglutathione (both at 0.01-100 muM) inhibited TCIPA and MMP-2 release from platelets and ***tumor*** cells. The inhibitory actions of S-nitroso-n-acetylpenicillamine and S-nitrosoglutathione were reversed by 1H-(1,2,4)oxadiazole(4,3)quinoxalin-1-one (0.01-30 muM), a selective inhibitor of the ***soluble*** ***guanylyl*** ***cyclase*** . We conclude that (a) human fibrosarcoma cells aggregate platelets via mechanism(s) that are mediated, in part, by MMP-2; (b) NO inhibits TCIPA, in part, by attenuating the release of MMP-2; and (c) these effects of NO are cGMP-dependent.

L12 ANSWER 8 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 2001:73055 BIOSIS
DN PREV200100073055
TI Nitric oxide-mediated inhibition of DNA repair potentiates oxidative DNA damage in cholangiocytes.
AU Jaiswal, Meeta; LaRusso, Nicholas F.; Shapiro, Richard A.; Billiar, Timothy R.; Gores, Gregory J. (1)
CS (1) Department of Medicine, Mayo Medical School, Clinic, and Foundation, Rochester, MN, 55905: gores.Gregory@mayo.edu USA
SO Gastroenterology, (January, 2001) Vol. 120, No. 1, pp. 190-199. print.
ISSN: 0016-5085.
DT Article
LA English
SL English
AB Background & Aims: Chronic inflammation, a risk factor for the development of bile duct ***cancer*** , induces inducible nitric oxide synthase (iNOS) with nitric oxide (NO) generation, which promotes oxidative damage of DNA, a process that probably is important in the initiation and progression of malignancies. Because inhibition of DNA repair is required for accumulation of oxidative DNA lesions, our aim was to determine if NO also inhibits repair of oxidative DNA damage. Methods: A cholangiocarcinoma cell line and a cholangiocyte cell line were transfected with iNOS. Results: Extracts from transfected but not untransfected cells were unable to repair 8-oxodeoxyguanine (8-oxodG); this effect was irreversible because addition of dithiothreitol to cell extracts had no effect. NO inhibition of 8-oxodG repair was blocked by NO scavengers but not by peroxynitrite scavengers or inhibitors of the ***soluble*** ***guanylyl*** ***cyclase*** /protein kinase G pathway. NO also potentiated hydrogen peroxide-induced DNA damage. Finally, immunohistochemistry in human liver samples uniformly demonstrated de novo expression of iNOS and the presence of 3-nitrotyrosine and 8-oxodG formation in the biliary epithelia of 30 patients with primary sclerosing cholangitis (a premalignant disease of the biliary tract) compared with controls. Conclusions: Collectively, these data implicate NO-mediated inhibition of 8-oxodG base excision DNA repair processes as a mechanism potentiating DNA damage in human inflammatory diseases involving the biliary tract.

L12 ANSWER 9 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 2000:417073 BIOSIS
DN PREV200000417073
TI Nitric oxide inhibits the ***tumor*** necrosis factor alpha-regulated endocytosis of human dendritic cells in a cyclic GMP-dependent way.
AU Paolucci, Clara; Rovere, Patrizia; De Nadai, Celine; Manfredi, Angelo A.; Clementi, Emilio (1)
CS (1) DIBIT-Scientific Institute San Raffaele, Via Olgettina 58, 20132, Milano Italy
SO Journal of Biological Chemistry, (June 30, 2000) Vol. 275, No. 26, pp. 19638-19644. print.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB ***Tumor*** necrosis factor-alpha (TNFalpha)-induced maturation of dendritic cells (DC), with down-regulation of their endocytic ability, has been reported to be mediated by the accumulation of the lipid messenger ceramide. We have now studied the effects and mechanisms of action of NO on endocytosis, investigated with fluorescein isothiocyanate-labeled dextran using human monocyte-derived DC, both immature and after treatment with TNFalpha. Exposure of DC to NO, released by either bystander phagocytes or NO donors, reversed the inhibition of endocytosis induced by TNFalpha. The intracellular accumulation of ceramide induced by TNFalpha was also inhibited by NO. In addition, NO was found to exert an inhibitory effect downstream of the TNFalpha-triggered ceramide accumulation, because NO donors reversed the inhibition of endocytosis induced by the cell-permeant C2-ceramide. These effects of NO were mimicked by the membrane-permeant cyclic GMP analogue, 8-Br cyclic GMP, and prevented by inhibition of the ***soluble*** ***guanylyl*** ***cyclase*** . At variance with rodents, the inducible isoform of the NO synthase was expressed neither in immature human DC nor after cell treatment with

TNFalpha, interferon-gamma, and lipopolysaccharide, suggesting that regulation of these cells depends on exogenous NO. NO, working through cyclic GMP, might therefore prolong the ability of human DC to internalize antigens at the site of inflammation and thus modulate the initial steps leading to antigen-specific immune responses.

L12 ANSWER 10 OF 31 MEDLINE
AN 2000460055 MEDLINE
DN 20344999 PubMed ID: 10884560
TI The mechanism of actions of 3-(5'-(hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1) on Ca(2+)-activated K(+) currents in GH(3) lactotrophs.
AU Wu S N; Hwang T; Teng C M; Li H F; Jan C R
CS Department of Medical Research and Education, Veterans General Hospital-Kaohsiung, 386, Ta-Chung 1st Road, Kaohsiung, Taiwan, ROC.. snwu@isca.vghks.gov.tw
SO NEUROPHARMACOLOGY, (2000 Jul 24) 39 (10) 1788-99.
Journal code: NZB; 0236217. ISSN: 0028-3908.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928
AB The effects of 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1), an activator of ***soluble*** ***guanylyl*** ***cyclase*** , on ionic currents have been assessed in rat pituitary GH(3) lactotrophs. In GH(3) cells bathed in normal Tyrode's solution, YC-1 (1 microM) reversibly suppressed the amplitude of the Ca(2+)-activated K(+) current (I(K(Ca))). YC-1 at a concentration above 10 microM produced a biphasic response in the amplitude of I(K(Ca)), i.e., an initial decrease followed by a sustained increase. When the pipette solutions were filled with high EGTA (10 mM), the YC-1-induced stimulatory effect on I(K(Ca)) was abolished. Over a similar concentration range, YC-1 also effectively inhibited the voltage-dependent K(+) current (I(K(V))) in GH(3) cells. The IC(50) value required for the inhibition of I(K(V)) by YC-1 was 1 microM. Unlike YC-1, 8-bromo cGMP did not inhibit I(K(Ca)). However, YC-1 (10 microM) did not affect the amplitude of L-type Ca(2+) current. In the cell-attached configuration, application of YC-1 (10 microM) to the bath did not change the single-channel conductance of the large-conductance Ca(2+)-activated K(+) (BK(Ca)) channels; however, it did increase the opening probability of BK(Ca) channels. In contrast, in the outside-out configuration, YC-1 (10 microM) significantly suppressed the opening probability of BK(Ca) channels. The present study shows dual effects of YC-1 on I(K(Ca)) in GH(3) cells. The YC-1-mediated stimulation of I(K(Ca)) may result from elevated cytosolic Ca(2+), whereas the inhibition of I(K(Ca)) and I(K(V)) by YC-1 appears to be direct and independent of the activation of ***soluble*** ***guanylyl*** ***cyclase*** . Caution thus needs to be used in attributing the YC-1-mediated response to the activation of ***soluble*** ***guanylyl*** ***cyclase*** .

L12 ANSWER 11 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 2000:294479 BIOSIS
DN PREV200000294479
TI Heme oxygenase-1 is a cGMP-inducible endothelial protein and mediates the cytoprotective action of nitric oxide.
AU Polte, Tobias; Abate, Aida; Dennery, Phyllis A.; Schroeder, Henning (1)
CS (1) School of Pharmacy, Martin Luther University, Wolfgang-Langenbeck-Str. 4, 06099, Halle (Saale) Germany
SO Arteriosclerosis Thrombosis and Vascular Biology, (May, 2000) Vol. 20, No. 5, pp. 1209-1215. print.
ISSN: 1079-5642.
DT Article
LA English
SL English
AB Inducible heme oxygenase (HO-1) has recently been recognized as an antioxidant and cytoprotective gene. By use of Western blotting, cell viability analysis, and antisense technique, the present study investigates the involvement of HO-1 in endothelial protection induced by the clinically used nitric oxide (NO) donor molsidomine (specifically, its active metabolite 3-morpholinosydnonimine (SIN-1)) and the second messenger cGMP. In bovine pulmonary artery endothelial cells, SIN-1 and S-nitroso-N-acetyl-D,L-penicillamine (SNAP) at 1 to 100 mumol/L induced the synthesis of HO-1 protein in a concentration-dependent fashion up to 3-fold over basal levels. HO-1 induction by SIN-1 was inhibited in the presence of the NO scavenger phenyl-4,4,5,5,-tetramethylimidazoline-1-oxyl-3-oxide and the ***soluble*** ***guanylyl*** ***cyclase*** inhibitor 1H-(1,2,4)oxadiazole(4,3-a)quinoxalin-1-one. 8-Bromo-cGMP (1 to 100 mumol/L) and dibutyryl cGMP (1 to 100 mumol/L) as well as the activator of particulate guanylyl cyclase atrial natriuretic peptide (1 to 100 nmol/L) produced increases in HO-1 protein similar to those produced by SIN-1. SIN-1 and 8-bromo-cGMP increased heme oxygenase activity (bilirubin formation). Cytoprotection by NO donors was abrogated in the presence of the heme oxygenase inhibitor tin protoporphyrin IX. Pretreatment of cells with a phosphorothioate-linked HO-1 antisense oligonucleotide prevented protection by SIN-1 or 8-bromo-cGMP against ***tumor*** necrosis factor-alpha cytotoxicity, whereas sense and scrambled HO-1 were without effect under these conditions. Our results show for the first time that HO-1 is a cGMP-sensitive endothelial gene and establish conclusively a causal relationship between HO-1 induction and endothelial protection by the NO/cGMP system. By targeting cytoprotective HO-1, NO donors may therefore be expected to induce antioxidant, antiatherogenic, and anti-inflammatory effects.

L12 ANSWER 12 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 2000:288920 BIOSIS
DN PREV200000288920
TI Involvement of nitric oxide synthase in the physiology and pathophysiology of facial nerve function and dysfunction.
AU Michel, Olaf (1); Hess, Alexander; Krolzig, Martin; Stennert, Eberhard; Addick, Klaus; Bloch, Wilhelm
CS (1) Department of Otorhinolaryngology, University of Cologne, Joseph-Stelzmann-Strasse 9, 50924, Cologne Germany
SO European Archives of Oto-Rhino-Laryngology, (April, 2000) Vol. 257, No. 4, pp. 188-192. print.
ISSN: 0937-4477.
DT Article
LA English
SL English
AB To date few reports have discussed the presence and function of nitric oxide (NO) in structures of the facial nerve. We performed nicotinamide adenine dinucleotide phosphate (NADPH-d)-diaphorase-histochemistry and immunohistochemistry on the intratemporal portion of the facial nerve, including the geniculate ganglion, of guinea pigs using specific antibodies to the three known isoforms of NO synthase and ***soluble*** ***guanylyl*** - ***cyclase*** (sGC). Normal facial nerves were compared to those treated intratympanically with bacterial lipopolysaccharides (LPS) and ***tumor*** necrosis factor-alpha (TNF-alpha). Both constitutive NOS isoforms and sGC could be detected in the bipolar ganglion cells of normal animals, while the inducible isoform (iNOS or NOS II) was not found. Endothelial NOS (NOS III) and sGC were present in blood vessels and were predominantly found in the perineurial sheath and less in the endoneurium. sGC could be detected in all fibers in a cross section of the facial nerve. LPS and TNF treatment led to the detection of iNOS in the perikaryia of the geniculate ganglion and the perineural sheath. These findings imply that NO may be involved in neurotransmission at least in the visceroafferent system. NO regulates vascular tone of nutrient blood vessels in the perineural sheath and endoneurium. The presence of sGC indicates that NO acts via its second messenger cGMP. NOS II expression may be a contributing factor to facial nerve palsy via two different mechanisms: NOS II-generated NO may lead to an overstimulation of the visceroefferent nerve fibers and motor fibers of the facial nerve. Dysregulation in facial nerve blood vessels could lead to edema and elevated pressure on the nerve within its osseous canal.

L12 ANSWER 13 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 2000:253850 BIOSIS
DN PREV200000253850
TI The beta2 subunit of ***soluble*** ***guanylyl*** ***cyclase*** contains a human-specific frameshift and is expressed in gastric carcinoma.
AU Behrends, Soenke (1); Vehse, Kai
CS (1) University Hospital of Eppendorf, Pharmakologisches Institut, Martinistrasse 52, D-20251, Hamburg Germany
SO Biochemical and Biophysical Research Communications, (April 29, 2000) Vol. 271, No. 1, pp. 64-69. print..
ISSN: 0006-291X.
DT Article
LA English
SL English
AB Soluble or nitric oxide (NO) stimulated guanylyl cyclases are obligate heme-containing heterodimers (alpha/beta). We report the full-length cDNA of the human ortholog of the rat beta2-subunit from human kidney. A database search yielded matches of the 3' non-coding sequence with previously unassigned expressed sequence tags from kidney and stomach signet ring cell carcinoma. PCR comparison of cDNA from stomach signet ring cell carcinoma and normal stomach tissue demonstrated beta2 subunit expression in ***cancer*** but not in normal tissue. On the cDNA level a frameshift deletion of one nucleotide was present in the novel human sequence which was confirmed on the genomic DNA level. In four closely related nonhuman primate species the frameshift deletion was absent while analysis of genomic DNA from different ethnic backgrounds revealed the uniform presence of the frameshift deletion in the human population.

L12 ANSWER 14 OF 31 MEDLINE
AN 1999130335 MEDLINE
DN 99130335 PubMed ID: 9929565
TI Ca2+ channel inhibition induced by nitric oxide in rat insulinoma RINm5F cells.
AU Grassi C; D'Ascenzo M; Valente A; Battista Azzena G
CS Institute of Human Physiology, Catholic University S. Cuore, Largo F. Vito 1, I-00168 Rome, Italy.. claudiograssi@hotmail.com
SO PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1999 Jan) 437 (2) 241-7.
Journal code: OZX; 0154720. ISSN: 0031-6768.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199903
ED Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990303
AB The effect of nitric oxide (NO) donors on high-voltage-activated Ca2+ channels in insulin-secreting RINm5F cells was investigated using the patch-clamp technique in the whole-cell configuration. Sodium nitroprusside (SNP, 2-400 microM) induced a dose-dependent reduction in Ba2+ currents with maximal inhibition of 58%. The IC50 for SNP was 45 microM. A different NO donor, (+/-)S-nitroso-N-acetylpenicillamine (SNAP, 500 microM), also produced a 50% decrease in current amplitude. When 200 microM SNP was administered together with the NO scavenger 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidozoline-1-oxyl-3-oxide (carboxy-PTIO, 300 microM), the Ba2+ current inhibition was lowered to 7%. Administration of 500 microM 8-bromoguanosine 3':5'-cyclic monophosphate sodium salt (8-Br-cGMP) mimicked the effects of SNP, causing a comparable decrease (56%) in peak-current amplitude. When ***soluble*** ***guanylyl*** ***cyclase*** was blocked by 10 microM 1H-[1,2,4]oxadiazole[4,3-a]quinoxalin-1-one (ODQ), the inhibitory effect of 200 microM SNP was reduced from 39% to 15%. The SNP-induced current decrease
was 36% of controls after the blockade of L-type Ca2+ channels and 30% in the presence of 2.5 microM omega-conotoxin-MVIIC. These data indicate that NO inhibits both L-type and P/Q-type Ca2+ channels in RINm5F cells, probably by an increase in the intracellular levels of cGMP. NO may then significantly influence the Ca2+-dependent release of hormones from secretory cells as well as that of neurotransmitters from nerve terminals.

L12 ANSWER 15 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 1999:294938 BIOSIS
DN PREV199900294938
TI Expression of inducible nitric oxide synthase (iNOS/NOS II) in the cochlea of guinea pigs after intratympanical endotoxin-treatment.
AU Hess, Alexander (1); Bloch, Wilhelm; Huverstuhl, Jochen; Su, Jiping; Stennert, Eberhard; Addicks, Klaus; Michel, Olaf
CS (1) Klinik und Poliklinik fuer Hals-, Nasen- und Ohrenheilkunde der Universitaet zu Koln, 50924, Cologne Germany
SO Brain Research, (May 29, 1999) Vol. 830, No. 1, pp. 113-122.
ISSN: 0006-8993.
DT Article
LA English
SL English
AB Since NO is believed to be involved in cochlear physiology, presence of the constitutive isoforms of nitric oxide synthase (NOS), and the target enzyme of NO, ***soluble*** ***guanylyl*** ***cyclase*** (sGC) in structures of the mammalian cochlea have been demonstrated. To date, no reports have been published regarding the detection of the inducible isoform (NOS II) in the cochlea. In order to show the capability of iNOS expression in cochlear tissue, a mixture of proinflammatory bacterial lipopolysaccharides (LPS) and ***tumor*** necrosis factor alpha (TNF-alpha) was injected into the tympanic cavity of guinea pigs, vs. saline-solution as control. Paraffin sections of LPS/TNF-alpha treated and saline-treated cochleae (6 h) were examined immunohistochemically with specific antibodies to neuronal, endothelial and inducible NOS and to sGC. Initiated expression of iNOS in the cochlea was observed in the wall of blood vessels of the spiral ligament (SL) and the modiolus, in supporting cells of the organ of Corti, in the limbus, in nerve fibers and in a part of the perikarya of the spiral ganglion after LPS/TNFalpha-treatment. iNOS was not detected in saline-treated control tissue. Expression of both constitutive NOS-isoforms (endothelial and neuronal NOS) and of sGC showed no significant differences in both experimental groups. Endothelial eNOS and neuronal bNOS were detected co-localized in ganglion cells, in nerve fibers, in cells of the SL and in supporting cells of the organ of Corti, but not in sensory cells. Strong labeling for bNOS became evident in the endosteum of the cochlea, while in the endothelium of blood vessels and in the epithelium of the limbus only eNOS could be labeled. sGC could be detected in SL, in supporting and sensory cells of the organ of Corti, in nerve fibers, ganglion cells, in the wall of blood vessels and in the limbus-epithelium. While small amounts of NO, generated by bNOS and eNOS, seem to support the cochlear blood flow and auditory function as well as neurotransmission, high amounts of iNOS-generated NO could have dysregulative and neurotoxic effects on the inner ear during bacterial and viral infections of the middle and inner ear.

L12 ANSWER 16 OF 31 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998364010 EMBASE
TI Rapid and delayed p42/p44 mitogen-activated protein kinase activation by nitric oxide: The role of cyclic GMP and tyrosine phosphatase inhibition.
AU Callsen D.; Pfeilschifter J.; Brune B.
CS Dr. B. Brune, University of Erlangen-Numberg, Faculty of Medicine, Loschgestrasse 8, 91054 Erlangen, Germany. mfm423@rzmail.uni-erlangen.de
SO Journal of Immunology, (1 Nov 1998) 161/9 (4852-4858).
Refs: 55
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LA English
SL English
AB The exposure of rat mesangial cells to cytokines promoted activation of the p42/p44 mitogen-activated protein kinase (MAPK). We identified a rapid and delayed phase of MAPK activation with distinctive activity increases at 5 to 15 min and 15 to 24 h. Rapid and late MAPK activation were attenuated by the redox-modulating agent N-acetylcysteine. Specifically, late-phase activation coincided with endogenous nitric oxide (NO) generation and in turn was suppressed by the NO synthase-blocking compounds diphenyliodonium or nitroarginine methyl ester. By using NO-liberating agents such as S- nitrosoglutathione and 3-morpholinosydnonimine, we investigated intermediary signaling elements of NO in promoting MAPK activation. Early and transient activation at 5 min was suppressed by the ***soluble*** ***guanylyl*** ***cyclase*** -blocking agent 1H-(1,2,4)-oxdiazolo-(4,3-.alpha.)-6-bromoquinoxazin1-one (NS 2028) and, moreover, was mimicked by the lipophilic cYClic GMP (cGMP) analogue 8-bromo- cGMP. In contrast, NO-mediated activation achieved within hours was unrelated to cGMP signaling. Late and persistent MAPK. Activation, induced by NO donors or endogenously generated NO, was found in association with inhibition of phosphatase activity. In vitro dephosphorylation of activated and immunoprecipitated p42/p44 by cytosolic phosphatases was sensitive to the readdition of NO and was found to be inhibited in cytosol of S-nitrosoglutathione-stimulated cells. Also, cells that had been exposed to cytokines for 24 h revealed a blocked phosphatase activity, which was successfully attenuated by the NO synthase inhibitor nitroarginine methyl ester and, therefore, was NO mediated. Conclusively, NO affects p42/p44 MAPK in rat mesangial cells twofold: rapid activation is cGMP mediated, whereas late activation is transmitted via inhibition of tyrosine dephosphorylation.

L12 ANSWER 17 OF 31 MEDLINE DUPLICATE 12
AN 1998049589 MEDLINE
DN 98049589 PubMed ID: 9388267
TI Nitric oxide inhibits apoptosis by preventing increases in caspase-3-like activity via two distinct mechanisms.
AU Kim Y M; Talanian R V; Billiar T R
CS Department of Surgery, College of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, USA.
NC GM-37753 (NIGMS)
GM-44100 (NIGMS)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Dec 5) 272 (49) 31138-48.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980122
Last Updated on STN: 20000303
Entered Medline: 19980108
AB Nitric oxide (NO) has emerged as an important endogenous inhibitor of apoptosis, and here we report that NO prevents hepatocyte apoptosis initiated by the removal of growth factors or exposure to TNFalpha or anti-Fas antibody. We postulated that the mechanism of the inhibition of apoptosis by NO would include an effect on caspase-3-like protease activity. Caspase-3-like activity increased coincident with apoptosis due to all three stimuli, and treatment with the caspase-3-like protease inhibitor N-acetyl-Asp-Glu-Val-Asp-aldehyde inhibited both proteolytic activity and apoptosis. Endogenous or exogenous sources of NO prevented the increase in caspase-3-like activity in hepatocytes. Exposure of purified recombinant caspase-3 to an NO or NO+ donor inhibited proteolytic activity. Dithiothreitol (DTT), but not glutathione, reversed the inhibition of recombinant caspase-3 by NO. When lysates from cells stimulated to express inducible NO synthase or cells exposed to NO donors were incubated in DTT, caspase-3-like activity increased to about 55% of cells not exposed to a source of NO. Similarly, administration of an NO donor to rats treated with TNFalpha and D-galactosamine also prevented the increase in caspase-3-like activity as measured in liver homogenates. The effect of the NO donor was reversed by about 50% if the homogenate was incubated with DTT. TNFalpha-induced apoptosis and caspase-3-like activity were also reduced in cultured hepatocytes exposed to 8-bromo-cGMP, and both effects were inhibited by the cGMP-dependent kinase inhibitor KT5823. The suppression in caspase-3-like activity in hepatocytes exposed to an NO donor was partially blocked by an inhibitor of ***soluble*** ***guanylyl*** ***cyclase*** , 1H-[1,2,4]oxadiazolo[4,3,-a]quinoxalin-1-one, (ODQ), while the incubation of these lysates in DTT almost completely restored caspase-3-like activity to the level of TNFalpha-treated controls. These data indicate that NO prevents apoptosis in hepatocytes by either directly or indirectly inhibiting caspase-3-like activation via a cGMP-dependent mechanism and by direct inhibition of caspase-3-like activity through protein S-nitrosylation.

L12 ANSWER 18 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 1998:117654 BIOSIS
DN PREV199800117654
TI The nitric oxide donor SIN-1 protects endothelial cells from ***tumor*** necrosis factor-alpha-mediated cytotoxicity: Possible role for cyclic GMP and heme oxygenase.
AU Polte, Tobias; Oberle, Stefanie; Schroeder, Henning (1)
CS (1) Sch. Pharmacy, Martin Luther Univ., Wolfgang-Langenbeck-Str. 4, 06099 Halle Germany
SO Journal of Molecular and Cellular Cardiology, (Dec., 1997) Vol. 29, No. 12, pp. 3305-3310.

ISSN: 0022-2828.
DT Article
LA English
AB In cultured endothelial cells, incubation with TNF-alpha (50 ng/ml) for 72 h markedly reduced viability of endothelial cells. A 6-h pre-incubation with the nitric oxide (NO) donor linsidomine (SIN-1, 10-150 muM) protected endothelial cells in a concentration-dependent manner and increased viability by up to 59% of control. The unmetabolized parent compound molsidomine and the NO-free metabolite of SIN-13-morpholinoiminoacetonitrile (SIN-1C) were without cytoprotective effect. Cytoprotection by SIN-1 was completely abolished by the NO scavenger 2-phenyl-4,4,5,5,-tetramethylimidazoline-1-oxyl-3-oxide (PTIO, 30 muM). A cytoprotective effect comparable to SIN-1 was observed when preincubating the cells with dibutyryl cyclic GMP (10-100 muM). Moreover, no protection by SIN-1 occurred in the presence of cycloheximide (1 muM) or 1H(1,2,4)oxadiazole(4.3-a)quinoxalin-1-one (ODQ, 0.1 muM), a selective inhibitor of ***soluble*** ***guanylyl*** ***cyclase*** . Tin protoporphyrin-IX (SnPP, 25 muM), an inhibitor of heme oxygenase, was found to attenuate SIN-1-induced cytoprotection. Our results demonstrate that SIN-1 produces a long-term endothelial protection against cellular injury by TNF-alpha, presumably via a cyclic GMP-dependent pathway leading to up-regulation of protective proteins such as heme oxygenase.

L12 ANSWER 19 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 14
AN 1997:315396 BIOSIS
DN PREV199799605884
TI Nitric oxide protects endothelial cells from ***tumor*** necrosis factor-alpha-mediated cytotoxicity: Possible involvement of cyclic GMP.
AU Polte, Tobias; Oberle, Stefanie; Schroeder, Henning (1)
CS (1) Dep. Pharmacol. Toxicol., Sch. Pharm., Martin Luther Univ., Wolfgang-Langenbeck-Str. 4, 06099 Halle Germany
SO FEBS Letters, (1997) Vol. 409, No. 1-2, pp. 46-48. ISSN: 0014-5793.
DT Article
LA English
AB In cultured endothelial cells, incubation with TNF-alpha (50 ng/ml) for 48 h markedly reduced viability of endothelial cells. A 6 h preincubation with Sper/NO (0.03- -1 mu-M) protected endothelial cells in a concentration-dependent manner and increased viability by 63% of control. The NO scavenger PTIO (30 mu-M) completely abolished cytoprotection by Sper/NO. A cytoprotective effect comparable to Sper/NO was observed when preincubating the cells with 8-bromo cyclic GMP (1-10 mu-M). Moreover, no protection by Sper/NO occurred in the presence of ODQ (0.1 mu-M), a selective inhibitor of ***soluble*** ***guanylyl*** ***cyclase*** . Our results demonstrate that NO produces a long-term endothelial protection against cellular injury by TNF-alpha, presumably via a cyclic GMP-dependent pathway.

L12 ANSWER 20 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:277194 BIOSIS
DN PREV199698833323
TI Hypotensive mechanisms of amifostine.
AU Ryan, Sean V.; Carrithers, Stephen L.; Parkinson, Scott J.; Skurk, Carsten; Nuss, Charles; Pooler, Patricia M.; Owen, Charles S.; Lefer, Allan M.; Waldman, Scott A. (1)
CS (1) Div. Clin. Pharmacol., Dep. Clin. Pharmacology, MOB 813, Thomas Jefferson University, Philadelphia, PA 19107 USA
SO Journal of Clinical Pharmacology, (1996) Vol. 36, No. 4, pp. 365-373. ISSN: 0091-2700.
DT Article
LA English
AB Amifostine, a chemo- and radioprotective agent developed as adjunctive therapy for malignancies, induces hypotension after approx 20% of patient administrations. This study examines the molecular mechanisms underlying hypotension induced by amifostine. Amifostine and its metabolite, WR-1065, induced dose-dependent hypotension in anesthetized rats that was not blocked by N-G-methyl L arginine (L-NAME), an NO synthase inhibitor. WR-1065 but not amifostine induced concentration-dependent relaxation of isolated rat aortic rings in an endothelium-independent fashion. Relaxation was not associated with increases in cGMP or cAMP and could not be blocked by L-NAME or indomethacin. Similarly, neither amifostine or WR-1065 activated adenylyl, particulate guanylyl, or ***soluble*** ***guanylyl*** ***cyclases*** . WR-1-65 relaxed rat aortic rings precontracted with norepinephrine, suggesting alpha-adrenergic blocking activity. However, neither amifostine nor WR-1-65 altered the ability of prazosin or phentolamine to bind to alpha-adrenergic receptors. Further, WR-1065 had no effect on receptor-mediated increases in intracellular calcium in BAL 17 murine B lymphocytes in vitro. Thus, hypotension after administration of amifostine is mediated by WR-1065 and appears to result from direct relaxation of vascular smooth muscle. Smooth muscle relaxation induced by WR-1-65 is not related to production of nitric oxide, prostaglandins, or cyclic nucleotides; alpha-adrenergic receptor antagonism; or interference with receptor-dependent increases in intracellular calcium. Administration of ephedrine, an efficacious adrenergic agonist, attenuated hypotension induced by amifostine in anesthetized rats and may be useful in alleviating hypotension associated with amifostine administration in patients.

L12 ANSWER 21 OF 31 MEDLINE DUPLICATE 15
AN 95382131 MEDLINE
DN 95382131 PubMed ID: 7544539
TI TNF-alpha and IFN-gamma induce expression of nitric oxide synthase in cultured rat medullary interstitial cells.
AU Lau K S; Nakashima O; Aalund G R; Hogarth L; Ujiie K; Yuen J; Star R A
CS Department of Physiology, University of Texas-Southwestern Medical School, Dallas 75235-8856, USA.
NC DK-01888 (NIDDK)
SO AMERICAN JOURNAL OF PHYSIOLOGY, (1995 Aug) 269 (2 Pt 2) F212-7. Journal code: 3U8; 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199509
ED Entered STN: 19951005
Last Updated on STN: 19960129
Entered Medline: 19950922
AB Cytokines increase the expression of the inducible (type II) nitric oxide synthase (NOS) in macrophages, liver, and renal epithelial cells. Previously, we found that cultured rat medullary interstitial cells (RMIC) contain high levels of ***soluble*** ***guanylyl*** ***cyclase*** . To determine whether these cells can also produce NO, we studied the effects of ***tumor*** necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) on NO production, NOS II mRNA, and NOS II protein expression. Both TNF-alpha and IFN-gamma, in the presence of a low concentration of the other cytokine, caused dose-dependent increases in NO production. Exposure to TNF-alpha and IFN-gamma stimulated the production of NOS II mRNA, as determined by Northern blotting. Restriction mapping of reverse transcription-polymerase chain reaction products indicated that normal cells contained macrophage NOS II, whereas cytokine-stimulated cells contained primarily vascular smooth muscle NOS II and some macrophage NOS II. The appearance of NOS II protein was demonstrated by Western blotting. RMIC cell guanosine 3',5'-cyclic monophosphate accumulation increased 129-fold in response to the cytokines. NOS inhibitors decreased nitrite production. We conclude that 1) TNF-alpha and IFN-gamma induce the expression of vascular smooth muscle NOS II and production of NO in RMIC, and 2) NO acts as an autocrine activator of the ***soluble*** ***guanylyl*** ***cyclase*** in RMIC.

L12 ANSWER 22 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:494292 BIOSIS
DN PREV199598508592
TI TNF-alpha and IFN-gamma induce expression of nitric oxide synthase in cultured rat medullary interstitial cells.
AU Lau, Kim S.; Nakashima, Osamu; Aalund, Gordon R.; Hogarth, Laurie; Ujiie, Kazutomo; Yuen, John; Star, Robert A. (1)
CS (1) Univ. Texas-Southwestern Med. Sch., 5323 Harry Hines Blvd., Dallas, TX 75235-8856 USA
SO American Journal of Physiology, (1995) Vol. 269, No. 2 PART 2, pp. F212. ISSN: 0002-9513.
DT Article
LA English
AB Cytokines increase the expression of the inducible (type II) nitric oxide synthase (NOS) in macrophages, liver, and renal epithelial cells. Previously, we found that cultured rat medullary interstitial cells (RMIC) contain high levels of ***soluble*** ***guanylyl*** ***cyclase*** . To determine whether these cells can also produce NO, we studied the effects of ***tumor*** necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) on NO production, NOS II mRNA, and NOS II protein expression. Both TNF-alpha and IFN-gamma, in the presence of a low concentration of the other cytokine, caused dose-dependent increases in NO production. Exposure to TNF-alpha and IFN-gamma stimulated the production of NOS II mRNA, as determined by Northern blotting. Restriction mapping of reverse transcription-polymerase chain reaction products indicated that normal cells contained macrophage NOS II, whereas cytokine-stimulated cells contained primarily vascular smooth muscle NOS II and some macrophage NOS II. The appearance of NOS II protein was demonstrated by Western blotting. RMIC cell guanosine 3',5'cyclic monophosphate accumulation increased 129-fold in response to the cytokines. NOS inhibitors decreased nitrite production. We conclude that 1) TNF-alpha and IFN-gamma induce the expression of vascular smooth muscle NOS II and production of NO in RMIC, and 2) NO acts as an autocrine activator of the ***soluble*** ***guanylyl*** ***cyclase*** in RMIC.

L12 ANSWER 23 OF 31 MEDLINE DUPLICATE 16
AN 95398620 MEDLINE
DN 95398620 PubMed ID: 7545388
TI Contributions of NO synthase and heme oxygenase to cGMP formation by cytokine and hemin treated brain capillary endothelial cells.
AU Vigne P; Feolde E; Ladoux A; Duval D; Frelin C
CS Institut de Pharmacologie Moleculaire et Cellulaire du CNRS, Universite de Nice-Sophia, Valbonne, France.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 Sep 5) 214 (1) 1-5.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199510
ED Entered STN: 19951020
Last Updated on STN: 19980206
Entered Medline: 19951012
AB Two mechanisms contribute to cGMP formation by ***soluble*** ***guanylyl*** ***cyclase*** (i) NO production by NO synthase and (ii) CO production by heme oxygenase. We analyze here the contributions of these two pathways to IL1, TNF, lipopolysaccharide and hemin treated brain capillary endothelial cells. Cytokines and LPS induced cGMP formation in manners that were completely prevented by LY 83,583, methylene blue and by cyclosporin A. They were partially inhibited by inhibitor of NO synthase. Cyclosporin A acts by a posttranscriptional mechanism. Cells constitutively expressed mRNAs for heme oxygenase-1. Expression was enhanced by hemin but not by IL1 or lipopolysaccharide. Induction of heme oxygenase-1 and its inhibition by Sn protoporphyrin IX had no effect on cGMP levels.

L12 ANSWER 24 OF 31 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94223927 EMBASE
DN 1994223927
TI Nitric oxide decreases oxidant-mediated hepatocyte injury.
AU Kuo P.C.; Stivka A.
CS Department of Surgery, Stanford University Medical Center,Stanford, CA 94305, United States
SO Journal of Surgical Research, (1994) 56/6 (594-600).
ISSN: 0022-4804 CODEN: JSGRA2
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LA English
SL English
AB Nitric oxide (NO) is a readily diffusible, short-lived free radical with a multitude of organ-specific regulatory functions. Within the hepatocyte, NO production is associated with inhibition of mitochondrial electron transport enzyme activity, activation of ***soluble*** ***guanylyl*** ***cyclase*** , and inhibition of glyceraldehyde-3-phosphate dehydrogenase. However, while NO can regulate a number of hepatocyte functions, it is unknown whether NO production is hepatoprotective or hepatotoxic. Using isolated rat hepatocytes in primary short-term culture, we investigated the role of cytokine-mediated NO production in toxin-induced hepatocyte injury. In a model of acetaminophen (AM) hepatotoxicity, inhibition of cytokine-mediated NO production potentiated AM injury. In the presence of an inhibitor of NO synthesis, N(G)- monomethyl-L-arginine (L-NMMA), hepatocyte release of aspartate aminotransferase was increased twofold in the presence of 4.0 and 8.0 mM AM ($P < 0.01$). In addition, in the presence of AM, cytokine-mediated NO production was increased by 75% over baseline ($P < 0.01$). Maximum NO synthesis occurred at an AM concentration of 2 mM. A potential mechanism for the hepatoprotective effect of NO centers on its role in glutathione (GSH) homeostasis. In the presence of increasing concentrations of AM, hepatocyte GSH stores decreased in parallel in both control and cytokine-stimulated hepatocytes (ANOVA, $P < 0.01$). When cytokine-stimulated hepatocytes were exposed to 50 .mu.M L-NMMA, NO release was ablated, while glutathione levels decreased by threefold in comparison to controls ($P < 0.01$). In the presence of increasing concentrations of AM, cytokine-treated cells exposed to 50 .mu.M L-NMMA exhibited significant decremental decreases in GSH levels ($P < 0.05$). These data suggest that inhibition of cytokine-mediated NO production potentiates AM hepatotoxicity by modulation of hepatocyte glutathione stores.

L12 ANSWER 25 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
17
AN 1995:33231 BIOSIS
DN PREV199598047531
TI ANF(1-28) is a potent suppressor of pro-opiomelanocortic (POMC) mRNA but a weak inhibitor of beta-EP-LI release from AtT-20 cells.
AU Tan, Tean T.; Yang, Zhiyu; Huang, Weiqing; Lim, Alan T. (1)
CS (1) Cell Biol. Unit, Mental Health Res. Inst. Victoria, Private Bag 3, Parkville, VIC 3052 Australia
SO Journal of Endocrinology, (1994) Vol. 143, No. 2, pp. R1-R4.
ISSN: 0022-0795.
DT Article
LA English
AB Controversies remain whether atrial natriuretic factor (ANF) may play a role in modulating the release of POMC derived peptides from pituitary corticotrophs. Employing AtT-20 mouse pituitary tumour cells, we report here the effects of rat ANF(1-28) and sodium nitroprusside (SNP), both of which augment cellular levels of cGMP through activating particulate and ***soluble*** ***guanylyl*** ***cyclases*** respectively, on the expression of POMC mRNA abundance. Furthermore, the cellular contents and secretion of (beta endorphin-like immunoreactivity) beta-EP-LI from these cultures were also examined. Whereas the abundance of POMC mRNA was found
to be markedly suppressed following 4h of incubation with rANP(1-28) (0.01 to 1 mu-M), SNP (0.1 to 10 mu-M) and dibutyryl-cGMP (1 to 100 mu-M) in a dose related manner, only a modest reduction in the release and cell contents of beta-EP-LI was found in some of these cultures. It is also of interest to note that in all the cases examined the inhibitory effect was associated with a significant suppression of cAMP levels in the cultures. Taken together, our present findings suggest that ANF may play a more important role in suppressing the production than the release of POMC related peptides from AtT-20 cells. Thus, it raises the possibility that hypothalamic ANF may likewise modulate the function of the pituitary-adrenal axis through exerting a greater effect on inhibiting the production than the secretion of pituitary ACTH.

L12 ANSWER 26 OF 31 MEDLINE
AN 93233621 MEDLINE
DN 93233621 PubMed ID: 7682650
TI New signaling mechanism of angiotensin II in neuroblastoma neuro-2A cells: activation of ***soluble*** ***guanylyl*** ***cyclase*** via nitric oxide synthesis.
AU Chaki S; Inagami T
CS Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232.
NC HL-14192 (NHLBI)
HL-35323 (NHLBI)
SO MOLECULAR PHARMACOLOGY, (1993 Apr) 43 (4) 603-8.
Journal code: NGR; 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199305
ED Entered STN: 19930604
Last Updated on STN: 19970203
Entered Medline: 19930518
AB We previously reported that angiotensin II (Ang II) increases cGMP content through a new Ang II receptor subtype that is distinct from both the AT1 and AT2 subtypes in differentiated Neuro-2A cells. In this study, the mechanism of the Ang II-stimulated cGMP increase was investigated in comparison with bradykinin- and atrial natriuretic factor (ANF)-stimulated cGMP increases in differentiated Neuro-2A cells. Ang II increased cGMP in differentiated Neuro-2A cells rapidly, with a maximal effect in 30 sec and a return to basal levels in 60 sec. Removal of extracellular Ca2+ or pretreatment with a membrane-permeable Ca2+ chelator [1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetraacetoxymethyl ester] attenuated Ang II-stimulated cGMP accumulation. Both the time course and Ca2+ dependency of the effect of Ang II were similar to those of the effect of bradykinin, which activates ***soluble*** ***guanylyl*** ***cyclase*** , but distinct from those of the effect of ANF, which activates particulate guanylyl cyclase. Methylene blue, an inhibitor of ***soluble*** ***guanylyl*** ***cyclase*** , attenuated the effects of Ang II and bradykinin but not that of ANF. LaCl3, a nonspecific Ca2+ blocker, prevented Ang II-stimulated cGMP accumulation. L-type Ca2+ channel blockers, nifedipine and diltiazem, or an N-type Ca2+ channel blocker, omega-conotoxin, failed to inhibit the effect of Ang II. Ang II had no effect on formation of 1,4,5-inositol trisphosphate or cAMP content, whereas bradykinin stimulated 1,4,5-inositol trisphosphate formation in differentiated Neuro-2A cells. Further, the nitric oxide synthase inhibitors NG-monomethyl-L-arginine and NG-nitro-L-arginine attenuated Ang II- and bradykinin-stimulated elevation of cGMP content but not that stimulated by ANF. The Ca2+ ionophore A23187 also stimulated cGMP formation and the effect was inhibited by the nitric oxide synthase inhibitors. These results indicate that the newly found Ang II receptor mediates cGMP formation through activation of ***soluble*** ***guanylyl*** ***cyclase*** and that the activation is mediated by nitric oxide, which is increased by Ca2+ influx via an ion channel distinct from the L-type and N-type Ca2+ channels.

L12 ANSWER 27 OF 31 MEDLINE
AN 92378682 MEDLINE
DN 92378682 PubMed ID: 1324680
TI Molsidomine inhibits the chemoattractant-induced respiratory burst in human neutrophils via a no-independent mechanism.
AU Ervens J; Seifert R
CS Institut fur Pharmakologie, Freie Universitat Berlin, Germany.
SO BIOCHEMICAL PHARMACOLOGY, (1992 Aug 18) 44 (4) 637-44.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199209
ED Entered STN: 19921009
Last Updated on STN: 20000303
Entered Medline: 19920921
AB 3-Morpholino-sydnonimine (SIN-1) is a NO-releasing compound which mimics the effects of cGMP through activation of ***soluble*** ***guanylyl*** ***cyclase*** . Its prodrug, molsidomine (SIN-10), does not release NO but does modulate various cell functions. These findings prompted us to study the effects of SIN-10 and SIN-1 on the respiratory burst in human neutrophils. SIN-10 was more effective than SIN-1 in inhibiting superoxide anion (O2-) formation induced by N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMet-Leu-Phe) and by C5a. The effects of SIN-1 and SIN-10 on O2- formation were additive or less than additive, indicating the sydnonimines acted through a common mechanism. The sydnonimines showed no effect on O2- formations induced by gamma-hexachlorocyclohexane, arachidonic acid and a phorbol ester. They did not inhibit O2- formation induced by xanthine oxidase, by autoxidation of pyrogallol and in a cell-free system from HL-60 leukemic cells. Neutrophils did not convert SIN-10 to SIN-1 as assessed by O2 consumption which accompanies NO release from SIN-1. The cell-permeant analogue of

cGMP, N2,2'-O-dibutyryl guanosine 3':5'-monophosphate (Bt2cGMP), and SIN-10 but not SIN-1 inhibited fMet-Leu-Phe-induced O2 consumption. SIN-1 and SIN-10 slightly enhanced agonist binding to formyl peptide receptors, whereas Bt2cGMP was inhibitory. The sydnonimines did not affect GTP hydrolysis of heterotrimeric regulatory guanine nucleotide-binding proteins in HL-60 membranes. SIN-1 but not SIN-10 stimulated ADP-ribosylation of a 39-kDa protein in the cytosol of HL-60 cells. SIN-10 reduced fMet-Leu-Phe-induced rises in cytosolic Ca2+ concentration in neutrophils. These data suggest that SIN-10 inhibits the respiratory burst via a NO-independent mechanism which may involve inhibition of rises in cytosolic Ca2+ concentration.

L12 ANSWER 28 OF 31 MEDLINE DUPLICATE 18
AN 93049874 MEDLINE
DN 93049874 PubMed ID: 1330642
TI Nitric oxide formation caused by Ca2+ release from internal stores in neuronal cell line is enhanced by cyclic AMP.
AU Reiser G
CS Physiologisch-Chemisches Institut, Universitat Tubingen, Germany.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1992 Sep 1) 227 (1) 89-93.
Journal code: EN6; 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199212
ED Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921204
AB The influence of an elevated level of cyclic AMP on the formation of nitric oxide was investigated in a neuronal cell line (108CC15; NG108-15), in which we had previously shown that nitric oxide mediates the activation of ***soluble*** ***guanylyl*** ***cyclase*** upon stimulation with the hormones bradykinin, endothelin, and serotonin. Maximal amplitude and duration of cyclic GMP response to bradykinin were about 2-fold greater in cells with cyclic AMP levels increased by forskolin pretreatment than in control cells with basal levels of cyclic AMP. Phosphodiesterase inhibitors (isobutylmethylxanthine or M&B 22,948 (zaprinast)) similarly increased the maximal amplitude of the cyclic GMP response to bradykinin, but, in contrast, slowed down the decay phase of the cyclic GMP response to a much greater extent. The cyclic GMP responses to bradykinin were suppressed with the same potency by L-arginine analogues in control and in forskolin-treated cells (IC50 of NG-monomethyl-L-arginine 2 microM, of nitro-L-arginine 0.7 microM). The transient rises of cyclic GMP levels induced by bradykinin and endothelin, which both cause release of Ca2+ from internal stores, were similarly enhanced by forskolin pretreatment. However, the transient cyclic GMP response to serotonin which is due to Ca2+ influx into the neuronal cell line via 5-hydroxytryptamine3 (5-HT3) receptors was not affected by raising the cyclic AMP levels by forskolin pretreatment. Thus, cyclic AMP seems to enhance nitric oxide formation which depends on Ca2+ release from internal stores.

L12 ANSWER 29 OF 31 MEDLINE
AN 92063859 MEDLINE
DN 92063859 PubMed ID: 1683279
TI L-arginine stimulates cyclic guanosine 3',5'-monophosphate formation in rat islets of Langerhans and RINm5F insulinoma cells: evidence for L-arginine:nitric oxide synthase.
AU Laychock S G; Modica M E; Cavanaugh C T
CS Department of Pharmacology and Therapeutics, State University of New York School of Medicine, Buffalo 14214.
NC AM-25705 (NIADDK)
SO ENDOCRINOLOGY, (1991 Dec) 129 (6) 3043-52.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199112
ED Entered STN: 19920124
Last Updated on STN: 19970203
Entered Medline: 19911227
AB L-Arginine (L-Arg) is metabolized by nitric oxide synthase to the reactive intermediate nitric oxide. Since nitric oxide stimulates guanylyl cyclase and cGMP synthesis, L-Arg effects on cGMP accumulation in isolated pancreatic islets of the rat and RINm5F insulinoma cells were determined. Both L-Arg and glucose stimulation increased islet cGMP levels, and glucose potentiated the response to L-Arg alone. A competitive inhibitor of L-Arg metabolism to nitric oxide, NG-monomethyl-L-arginine, reduced glucose- and L-Arg-stimulated insulin release and glucose-induced increases in cGMP; however, basal insulin release was slightly increased. D-Arg and L-ornithine did not affect islet cGMP levels, although insulin release was stimulated. RINm5F cell cGMP levels and insulin release increased in response to L-Arg in a concentration- and time-related manner, whereas glucose and L-histidine were without effect. 8-Bromo-cGMP also slightly increased RINm5F cell insulin release. Sodium nitroprusside as a source of nitric oxide increased RINm5F cell cGMP production. Methylene blue and LY83583, inhibitors of ***soluble*** ***guanylyl*** ***cyclase*** activation, reduced RINm5F cell cGMP levels in the presence and absence of L-Arg; LY83583 also reduced glucose-stimulated cGMP levels in islets. Insulin release by glucose and L-Arg was also inhibited by methylene blue and LY83583 in islets. We conclude that glucose and L-Arg stimulate guanylyl cyclase activity and cGMP formation in beta-cells at least in part through metabolism to the reactive intermediate nitric oxide. However, neither nitric oxide nor cGMP synthesis is obligatory for insulin secretion.

L12 ANSWER 30 OF 31 MEDLINE
AN 90318346 MEDLINE
DN 90318346 PubMed ID: 2370855
TI Hormone-induced biosynthesis of endothelium-derived relaxing factor/nitric oxide-like material in N1E-115 neuroblastoma cells requires calcium and calmodulin.
AU Forstermann U; Gorsky L D; Pollock J S; Ishii K; Schmidt H H; Heller M; Murad F
CS Abbott Laboratories, Abbott Park, Illinois 60064.
NC AR 08080 (NIAMS)
DK 30787 (NIDDK)
HL 28474 (NHLBI)
SO MOLECULAR PHARMACOLOGY, (1990 Jul) 38 (1) 7-13.
Journal code: NGR; 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199008
ED Entered STN: 19900921
Last Updated on STN: 19970203
Entered Medline: 19900821
AB Stimulation of ***soluble*** ***guanylyl*** ***cyclase*** in rat fetal lung fibroblasts (RFL-6 cells) was used as a sensitive assay for endothelium-derived relaxing factor/nitric oxide (EDRF/NO) formation. Intact N1E-115 cells released an EDRF/NO-like material that enhanced cyclic GMP levels in RFL-6 cells. The synthesis of this substance could be stimulated with the receptor agonist neurotensin (10 microM) or by addition of the EDRF/NO substrate L-arginine (100 microM). In Ca2(+)-free Locke's solution, stimulation of EDRF/NO production by both neurotensin and L-arginine was abolished. The EDRF/NO-synthesizing activity was localized in the cytosol of N1E-115 cells. The activity was lost after boiling and it was highly sensitive to Ca2+ with the major increase in activity occurring between 100 and 500 nM Ca2+. L-Arginine and NADPH were required for maximal synthesis of EDRF/NO by the enzyme(s). The synthesis of EDRF/NO was inhibited by the following antagonists of calmodulin-regulated functions (with the approximate IC50 values given in parentheses): calmidazolium (7 microM), trifluoperazine (10 microM), fendiline (80 microM), W-7 (N-[6-aminohexyl]-5-chloro-1-naphthalenesulfonamide) (120 microM), and compound 48/80 (3 micrograms/ml). The EDRF/NO-synthesizing activity was partially purified from N1E-115 cytosol by DE 52 anion exchange chromatography. The activity was eluted with 0.1 M KCl. The enzyme(s) showed very little activity in the presence of L-arginine (100 microM) and NADPH (100 microM), but the activity could be fully restored by addition of exogenous calmodulin (EC50, approximately 2 units/ml). At 0.3 M KCl, a fraction eluted from the DE 52 column that was also able to fully restore the EDRF/NO-synthesizing activity. Thus, this fraction is likely to contain the endogenous Ca2(+)-binding protein. It is concluded that the activity of the EDRF/NO-synthesizing enzyme(s) in N1E-115 neuroblastoma cells is regulated by Ca2+ and calmodulin.

L12 ANSWER 31 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
19
AN 1978:123157 BIOSIS
DN BA65:10157
TI COMPARISON OF CYCLIC AMP AND CYCLIC GMP LEVELS CYCLASES AND PHOSPHO DI
ESTERASES IN MORRIS HEPATOMAS AND LIVER.
AU HICKIE R A; THOMPSON W J; STRADA S J; COUTURE-MURILLO B; MORRIS H P;
ROBISON G A
CS DEP. PHARMACOL., FAC. MED., UNIV. SASK., HEALTH SCI. BUILD., SASKATOON,
SASK. S7N OWO, CAN.
SO CANCER RES, (1977) 37 (10), 3599-3606.
CODEN: CNREA8. ISSN: 0008-5472.
FS BA; OLD
LA English
AB As a test of the hypothesis that cell proliferation is regulated by opposing effects of cyclic AMP (cAMP) and cGMP, the levels of these cyclic nucleotides were investigated in a rapidly growing [rat] hepatoma (7288ctc), 2 intermediate growth rate tumors [5123tc (h) and 5123C], 1 slow growing hepatoma (7794A), host liver and normal liver. Changes in cyclic nucleotide levels were also compared to alterations in activities of the soluble and particulate cyclases and phosphodiesterases in these tissues. In hepatoma 7288ctc the cAMP content was slightly lower than in normal liver (12%), whereas the cGMP levels were > 4-fold higher. The cAMP levels of 5123tc (h) and 5123C were 20-27% lower, whereas the cGMP levels were 25-33% higher than those of normal liver. For 7794A the cAMP content was 42% higher than that in normal liver, whereas the cGMP levels were 75% higher. In host livers the cAMP levels were usually higher than those in normal liver (22-47%) in animals bearing the rapidly growing and intermediate growth rate hepatomas. Host liver cGMP levels also tended to be 17-33% higher than those of normal liver. Although the cGMP/cAMP ratios are higher in hepatomas than in normal liver, there is no direct correlation between ***tumor*** growth rate and cyclic nucleotide

content or the corresponding cGMP/cAMP ratios. Changes in enzyme activities common to all 4 hepatomas included reduced activities of the total particulate cAMP phosphodiesterases as well as depressed activities of ***soluble*** ***guanylyl*** ***cyclase*** and particulate cGMP phosphodiesterase. The responsiveness of adenylyl cyclase to glucagon was impaired to a greater degree in the rapid- and intermediate growth rate tumors than in the slow growing one. This observation confirms previous findings of other workers in different hepatomas. The total activities of the apparent high affinity (low-Km) cAMP phosphodiesterase were substantially lower than those of normal liver in 7288ctc, 5123C and 7794A but were similar to those of liver in 5123tc (h). Some of the particulate fractions of the latter ***tumor*** actually had specific activities that exceeded those of normal liver. The cGMP/cAMP ratios observed in this study coincide more closely with specific changes in activities of the cyclases and/or phosphodiesterases than with differences in hepatoma growth rate.

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FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 16:24:08 ON 24 APR 2002
L1 567 S BK CHANNEL
L2 726 S BK CHANNELS
L3 929 S L1 OR L2
L4 0 S L3 AND DRUG DELIVER?
L5 0 S L3 AND SOLUBLE GUANYLYL CYCLASE
L6 1927 S SOLUBLE GUANYLYL CYCLASE?
L7 0 S L6 AND L3
L8 0 S L6 AND DRUG DELIVER
L9 1 S L6 AND DRUG DELIVER?
L10 61 S L6 AND (TUMOR OR CANCER OR GLIOMA)
L11 1 S L6 AND BLOOD BRAIN BARRIER?
L12 31 DUP REM L10 (30 DUPLICATES REMOVED)

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---Logging off of STN---

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Executing the logoff script...

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COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		119.54	119.75

STN INTERNATIONAL LOGOFF AT 17:20:54 ON 24 APR 2002

WEST Search History

DATE: Tuesday, April 23, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,DWPI; PLUR=YES; OP=ADJ		
L7	L6 and (brain or tumor)	12	L7
L6	nitric oxide same drug deliver$	40	L6
L5	soluble guanylyl cyclase activator	1	L5
L4	L3 and brain	14	L4
L3	drug deliver$ and potassium channel opener	27	L3
L2	soluble guanylyl cyclase and (brain or blood tumor barrier)	19	L2
L1	soluble guanylyl cyclase	33	L1

END OF SEARCH HISTORY